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FRANKLIN RESEARCH CENTER

DIVISION OF ARVIN/CALSPAN

THE SYNTHESIS OF POTENTIAL PARASITIC DRUGS

MIDTERM REPORT

MAY 1989

VALLEY FORGE CORPORATE CENTER 2600 MONROE BOULEVARD NORRISTOWN, PA 19403 TEL. (215) 666-3000

A: _____

THE SYNTHESIS OF POTENTIAL PARASITIC DRUGS

MIDTERM REPORT

MAY 1989

E. A. Nodiff, S. Chattopadhyay and K. Tanabe

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-88-C-8106

FRANKLIN RESEARCH CENTER
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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Distribution authorized to U. S. Government agencies only; proprietary information; May 1989
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: Franklin Research Center; 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): Valley Forge Corporate Center, 2600 Monroe Blvd., Norristown, PA 19403	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: U. S. Army Medical Research & Development Command; 8b. OFFICE SYMBOL (If applicable): SGRD-RMI-S	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: DAMD17-88-8106
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
62770A	3MI 62770A870	AJ	016

11. TITLE (Include Security Classification)

The Synthesis of Potential Antiparasitic Drugs (U)

12. PERSONAL AUTHOR(S)

Nodiff, Edward A.; Chattopadhyay, Sankar; Tanabe, Keiichi

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Midterm	FROM 88/4/1 TO 89/3/31	1989, May	67

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
07	03		Antiparasitic Drugs, Malarial, Primaquine, SAR, 8-Aminoquinolines, Blood Schizontocides, Tissue Schizontocides, Synthesis, RAI; (KT)
06	03		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

During the period from 1 April 1988 to 31 March 1989, we submitted to WRAIR 8 target compounds (Table I) and 15 intermediates (Table II). A number of additional syntheses are in progress (Table III). In earlier work, we prepared a series of primaquines with a methyl group at position 4 and a phenylalkoxy group at position 5. These compounds combined low toxicity with a unique dual efficacy against the blood and tissue forms of the malarial parasite. (Tables VI and VII). In the past year, we have attempted to enhance this series by attaching various substituents to the phenyl portion of the 5-phenylalkoxy group. Screening data for the new compounds are still too sparse for SAR conclusions (Tables IV & V) While awaiting additional data, we have started work on another group of primaquines. These derivatives will have an alkoxy, phenoxy or benzyloxy group at position 5, a methyl group at positions 3 or 4 and a methoxy or methyl group at position 2. Keywords:

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ OTIC USERS	UNCLASSIFIED

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
MARY FRANCES ROSTIAN	301-663-7325	SGRD-RMI-S

DD Form 1473, JUN 86 Previous editions are obsolete. SECURITY CLASSIFICATION OF THIS PAGE

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EA Hook 4/26/89

PI - Signature DATE

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INTRODUCTION

P. falciparum and P. vivax cause 95% of human malaria. P. falciparum has no persistent liver forms and thus no potential for relapse; it can be radically cured with a blood schizontocide. P. vivax does have persistent liver forms which can cause relapse by intermittent re-invasion of cleared blood. Radical cure of vivax malaria therefore requires a blood and a tissue schizontocide. Unfortunately, the antimalarial chemotherapeutic picture is bleak. Many clinical blood schizontocides are available but they are obsolescent because of the facility with which P. falicparum generates resistant strains. For example, mefloquine, the best of the new blood schizontocides, has already encountered resistance, in Thailand and Tanzania, while still in field trials. In stark contrast to the abundance of blood schizontocides, there is only a single drug, primaquine, in general use as a tissue schizontocide (antirelapse drug). Primaquine is also a gemetocytocide and a sporontocide and is relatively slow to select resistant strains. However, primaquine is far from the ideal drug; it is a poor blood schizontocide and it has a therapeutic index low enough to make its use hazardous.

In earlier work, we prepared a series of primaquines with an alkoxy group at position 5 and a methyl group at position 4. These compounds were extremely active as blood and tissue schizontocides but were toxic at the upper half of the dosage range (80-[illegible]0 mg/kg). We were subsequently able to dramatically attenuate the toxicity of these compounds, with minimal activity loss, by attaching a phenyl group to the terminal carbon of the 5-alkoxy group. The compounds with and without the terminal phenyl are compared in Tables VI and VII. In the past year, we have attempted to further enhance this series by attaching various substituents to the terminal phenyl group. Screening data for the new compounds (Scheme 1) are still too sparse for SAR conclusions (Tables IV and V). While awaiting additional data, we have started work on another group of primaquines (Schemes 4-7). These derivatives will have an alkoxy, phenoxy or benzyloxy group at position 5, a methyl group at positions 3 or 4 and a methoxy or methyl group at position 2.

Contract No. DAMD17-88-C-8106

TABLE I

TARGET COMPOUNDS SUBMITTED TO WRAIR

(1 April 1988 - 31 March 1989)

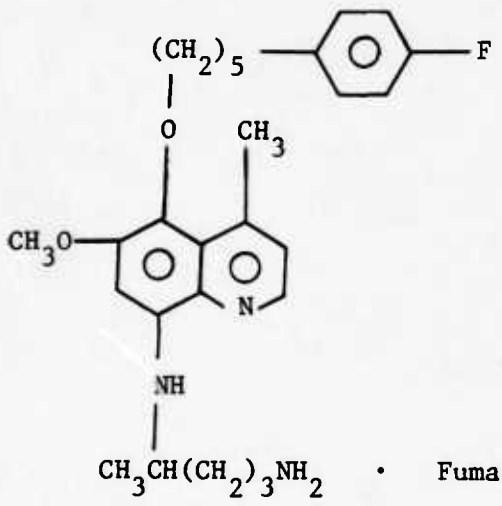
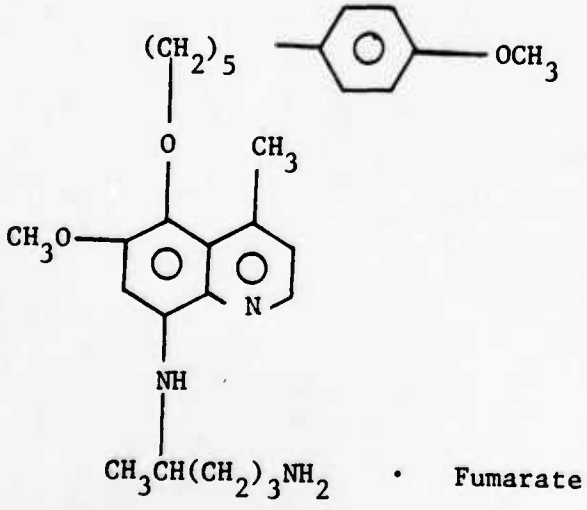
Structure	Quantity, g.	FRC Code	WR Number
	2.57	SAN-76	BL 52785
	2.4	SAN-93	BL 53522

TABLE I, CONTINUED

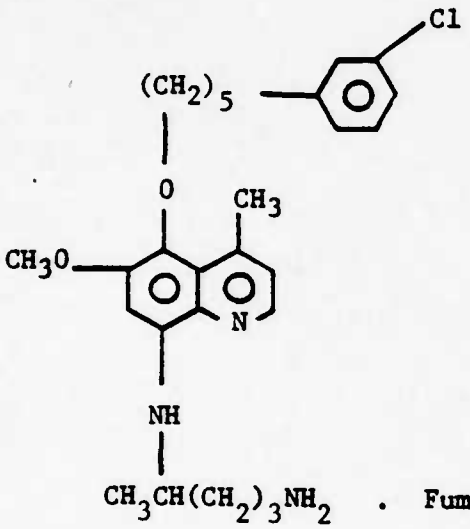
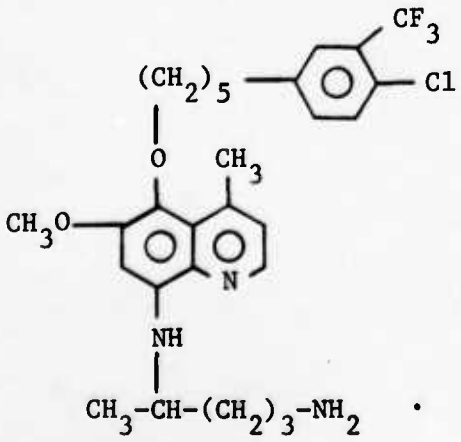
Structure	Quantity, g.	FRC Code	WR Number
	2.2	KT-1756	BL 54350
	1.8	II-SAN-22	BL 54627

TABLE I, CONTINUED

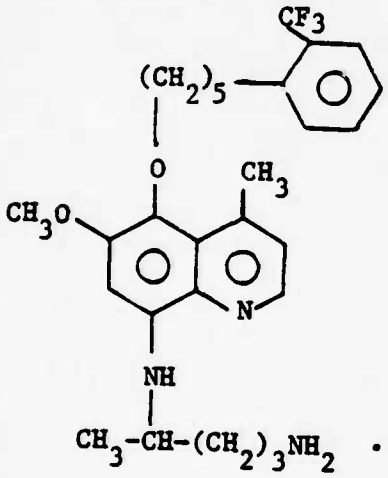
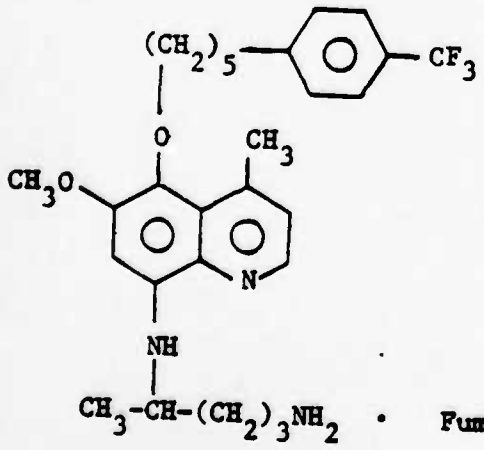
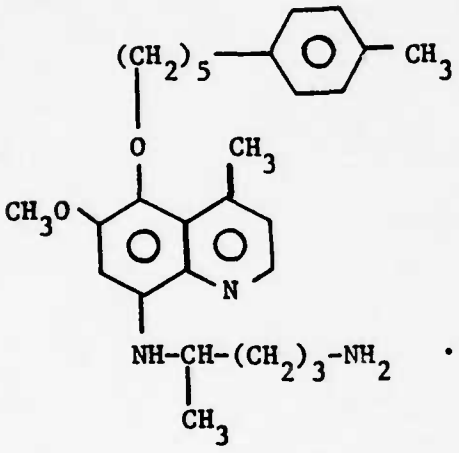
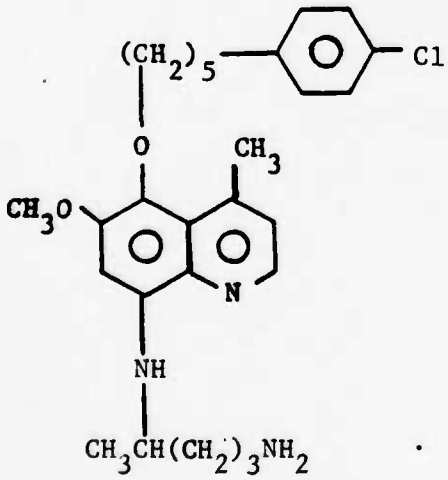
Structure	Quantity, g.	FRC Code	WR Number
 Fumarate	2.1	II-SAN-36	BL 54967
 Fumarate	2.8	II-SAN-47	BL 55384

TABLE I, CONTINUED

Structure	Quantity, g.	FRC Code	WR Number
 · Fumarate	5.5	II-SAN-59	BL 55820
 · Fumarate	2.57	III-SAN-1	BL56925

Contract No. DAMD17-88-C-8106

TABLE II

INTERMEDIATES SUBMITTED TO WRAIR

(1 April 1988 - 31 March 1989)

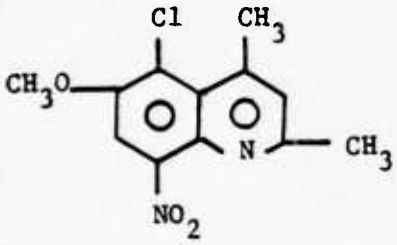
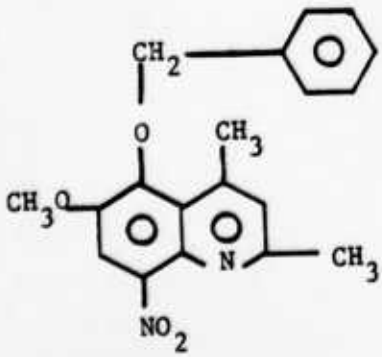
Structure	Quantity, g.	FRC Code	WR Number
	0.5	KT-1762	BL 54538
	0.5	KT-1759	BL-54529

TABLE II, Continued

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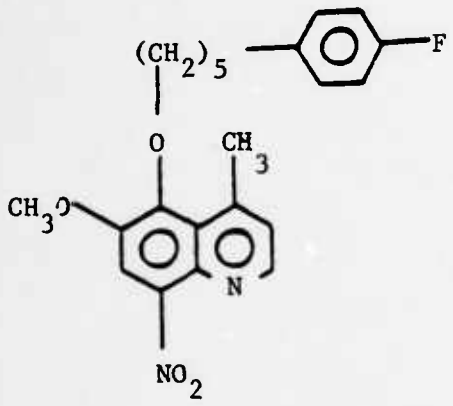
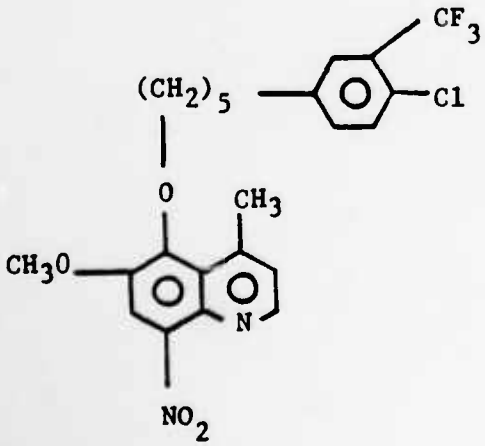
	0.5	SAN-65	BL 52454
	0.5	II-SAN-7	BL 54305

TABLE II, Continued

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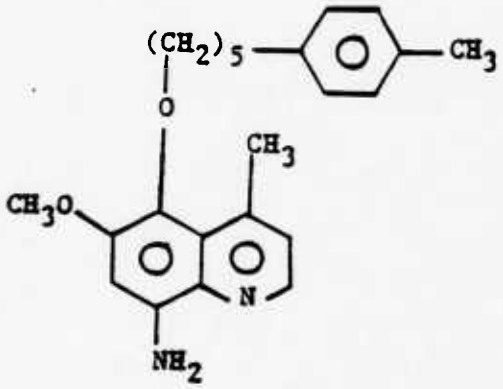
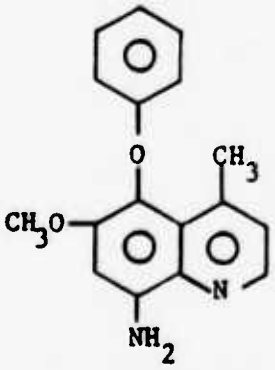
	0.5	II-SAN-55	BL 55900
	0.5	KT-1769	BL 55393

TABLE II, Continued

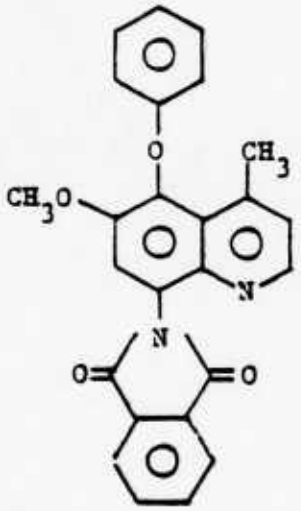
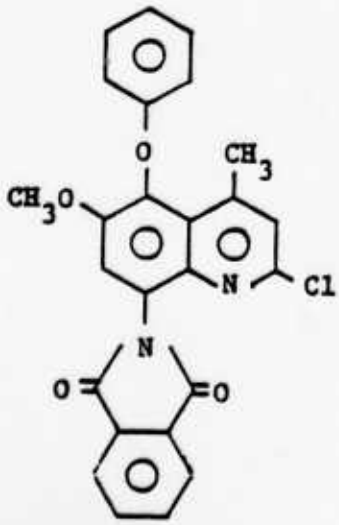
Structure	Quantity, g.	FRC Code	WR Number
	0.5	KT-1772	BL 55553
	0.5	KT-1775	BL 55946

TABLE II, Continued

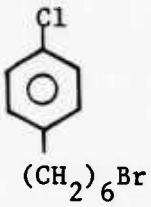
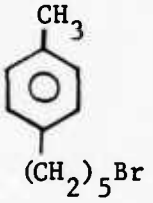
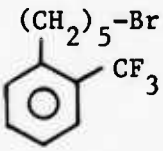
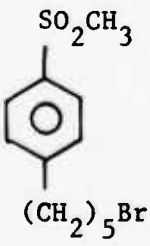
Structure	Quantity, g.	FRC Code	WR Number
	0.5	KT-1749	BL 53291
	0.5	II-SAN-49D	BL 55937
	0.5	II-SAN-28C	BL 54798
	0.5	II-SAN-79	BL56201

TABLE II, CONTINUED

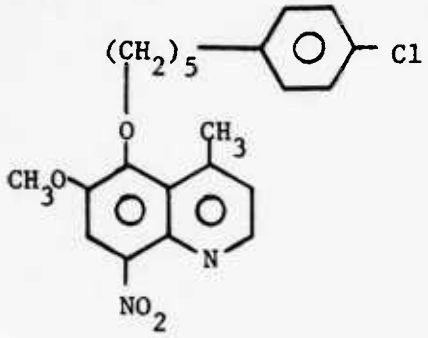
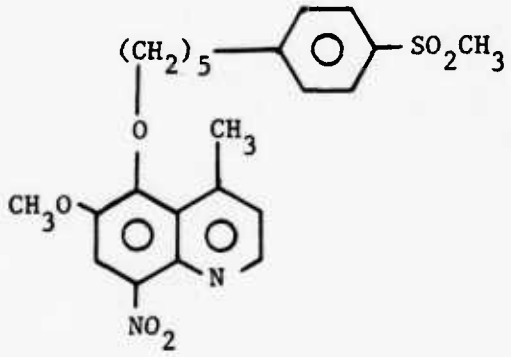
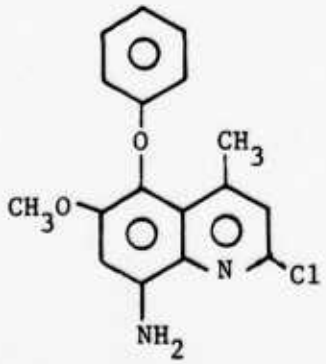
Structure	Quantity, g	FRC Code	WR Number
	0.5	III-SAN-9	BL 57057
	0.5	III-SAN-8	BL 57048
	0.5	KT-1781	BL 56416

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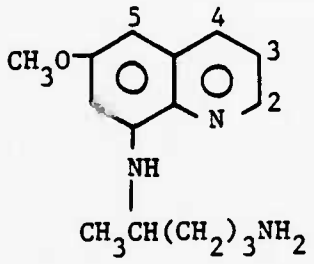
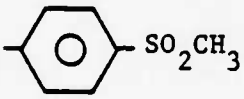
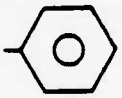
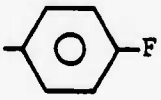
TABLE III

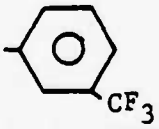
TARGET COMPOUNDS IN PROGRESS

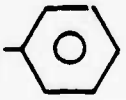


1. 4-CH_3, 5-O-$(CH_2)_5$- 

2. 4-CH_3, 2-CH_3O, 5-O- 

3. 4-CH_3, 2-CH_3O, 5-O- 

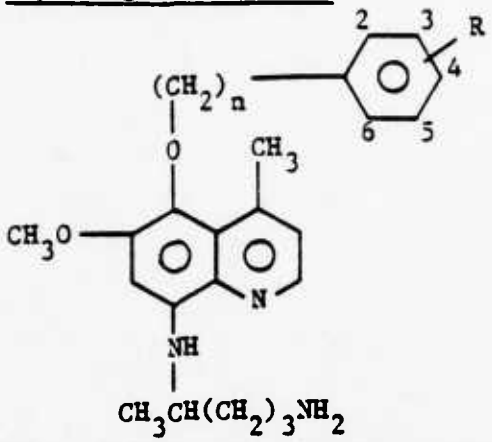
4. 3-CH_3, 2-CH_3O, 5-O- 

5. 4-CH_3, 2-CH_3O, 5-O-CH_2- 

BIOLOGY

TABLE IV

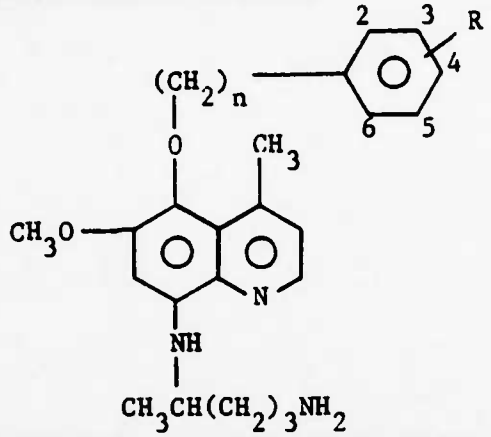
INFLUENCE OF SUBSTITUENTS ON THE PHENYL GROUP OF 5[ω-(PHENYL)ALKOXY]PRIMAQUINES
BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY
(P. berghei, Mouse)



No.	R	n	Cures (C), Toxic Deaths (T) or Δ MST Dose, mg/kg							
			5	10	20	40	80	160	320	640
BL 09293	H	5		3C	4C	5C	5C	5C	3C	1C
BL 50076	3-Cl	5		4C	5C	5C	5C	3C	1C	3C
BL 56925	4-Cl	5				Pending				
BL 54967	2-CF_3	5			3C	5C	5C	5C	5C	5C
BL 49439	3-CF_3	5		2C	5C	5C	5C	5C	3C	
BL 55384	4-CF_3	5				5C		5C		3C
BL 52785	4-F	5	1C	3C	4C	5C	5C	3C	2C	2T
BL 53522	4-OCH_3	5	8.1	5C	5C	5C		4C		3.0
BL 55820	4-CH_3	5				Pending				
BL 50236	3,5-$(CF_3)_2$	5	4.7	9.1	4C	5C	5C	5C	5C	5C
BL 54627	4-Cl,3-CF_3	5	7.6	1C	4C	5C		5C		4C,1T
BL 09962	H	6	5.9	1C	3C	4C	4C	3C	3C	4C
BL 30841 (BL-48825)	3-Cl	6	7.5	1C	4C	4C	5C	5C	5C	5C
BL 49448	3-CF_3	6		1C	4C	5C	5C	5C	5C	
BL 45137	2,3-Benzo	6		5.7	2C	5C	5C	5C	5C	

TABLE V

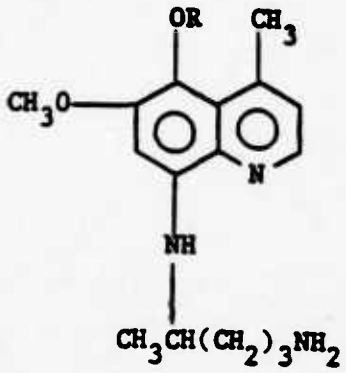
INFLUENCE OF SUBSTITUENTS ON THE PHENYL GROUP OF 5[ω-(PHENYL)ALKOXY]PRIMAQUINES RADICAL CURATIVE ANTIMALARIAL ACTIVITY (P. cynomolgi, Rhesus)



No.	R	n	Cures /No. of Animals Dose, mg/kg				
			0.1	0.316	1.0	3.16	10.0
BL 09293	H	5	1/2	4/4	2/2		
BL 50076	3-Cl	5		Pending			
BL 54967	2-CF_3	5		Pending			
BL 49439	3-CF_3	5		Pending			
BL 55384	4-CF_3	5		Pending			
BL 52785	4-F	5		Pending			
BL 53522	4-OCH_3	5		Pending			
BL 55820	4-CH_3	5		Pending			
BL 50236	3,5-$(CF_3)_2$	5		Pending			
BL 54627	4-Cl,3-CF_3	5		Pending			
BL 09962	H	6	0/2	4/4	2/2		
BL 30841 (BL 48825)	3-Cl	6		1/3	3/3		
BL 49448	3-CF_3	6		2/3	2/2	3/3	
BL 45137	2,3-Benzo	6		0/2	2/2	2/2	

TABLE VI

COMPARISON OF 5-ALKOXY AND 5-PHENYLALKOXYPRIMAQUINES BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY (P. berghei, Mouse)



No.	R	Cures (C), Toxic Deaths (T), Alive (A)* Dose, mg/kg							
		5	10	20	40	80	160	320	640
BJ 90650	$CH_3(CH_2)_2$	1C	1C	3C	3T		5T		5T
BK 51541	C_6H_5-$(CH_2)_3$	1C	5C	4C	4C	3C	5T	5T	5T
BJ 92565	$CH_3(CH_2)_3$		11.0	5C	3C	4T	5T	5T	5T
BL 21342	C_6H_5-$(CH_2)_4$	7.6	2C	4C	4C	5C	3C	0.4	0.0
BJ 51779	$CH_3(CH_2)_4$	5C	5C	4C	1C	2T	4T	5T	5T
BL 09293	C_6H_5-$(CH_2)_5$	7.9	3C	4C	5C	5C	5C	3C	1C
BH 89438 (WR 242,511)	$CH_3(CH_2)_5$	1C	1C	5C	5C	4C	3T	5T	5T
BL 09962	C_6H_5-$(CH_2)_6$	5.9	1C	3C	4C	4C	3C	3C	4C
BJ 45691	$CH_3(CH_2)_6$	3C	3C	5C	4C	2C	1T	5T	5T
BL 20434	C_6H_5-$(CH_2)_7$	2C	5C	5C	5C	5C	5C	5C	5C

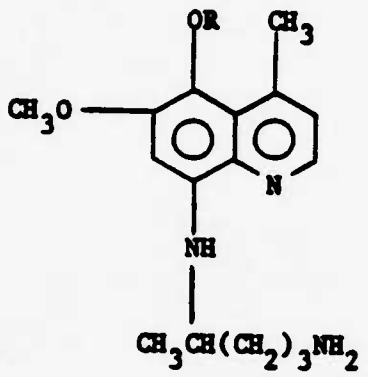
Continued on next page

Table VI - Continued

No.	R	Cures (C), Toxic Deaths (T), Alive (A) Dose, mg/kg							
		5	10	20	40	80	160	320	640
BK 39429	$CH_3(CH_2)_7$	12.0	5C	5C	5C	5C	2C	0.4	2T
BL 22349	$C_6H_5-(CH_2)_8$	5.7	1C	2C	5C	5C	5C	5C	5C
BK 22791	$CH_3(CH_2)_8$	9.7	2C	3C	5C	5C	4C	4C	4C
BL 30896	$C_6H_5-(CH_2)_9$		1C	8.5	2C	4C	5C	5C	3C

TABLE VII

COMPARISON OF
5-ALKOXY AND 5-PHENYLALKOXYPRIMAQUINES
RADICAL CURATIVE ANTIMALARIAL ACTIVITY (DB)
(P. cynomolgi, Rhesus)



No.	R	Cures /No. of Animals Dose, mg/kg				
		0.1	0.316	1.0	3.16	10.0
BJ 90650	$CH_3(CH_2)_2$	0/2	2/2	1/1		
BK 51541	$C_6H_5-(CH_2)_3$	1/2		2/2		T
BJ 92565	$CH_3(CH_2)_3$	0/2	2/2	1/1		
BL 21342	$C_6H_5-(CH_2)_4$	0/3	1/2	4/4		
BJ 51779	$CH_3(CH_2)_4$	3/4		2/2		
BL 09293	$C_6H_5-(CH_2)_5$	1/2	4/4	2/2		
BH 89438 (WR 242,511)	$CH_3(CH_2)_5$	5/5	3/3	1/1	0/1	
BL 09962	$C_6H_5-(CH_2)_6$	0/2	4/4	2/2		
BJ 45691	$CH_3(CH_2)_6$	0.2	2/2	4/4		
BL 20434	$C_6H_5-(CH_2)_7$	0/2	0/4	3/3		

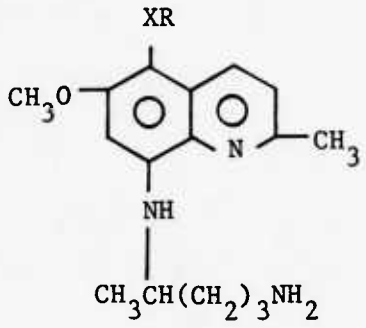
Continued on next page

Table VII - Continued

No.	R	Cures /No. of Animals				
		Dose, mg/kg				
		0.1	0.316	1.0	3.16	10.0
BK 39429	$CH_3(CH_2)_7$		0.1	1/1		T
BL 22349	$C_6H_5-(CH_2)_8$			Pending		
BK 22791	$CH_3(CH_2)_8$	0/2	0/2	1/1		T
BL 30896	$C_6H_5-(CH_2)_9$		0/3	0/2	2/2	

TABLE VIII

COMPARISON OF 5-PHENYLTHIO, 5-ALKYLTHIO AND 5-ALKOXYPRIMAQUINES BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY (P. berghei, Mouse)



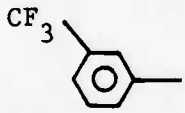
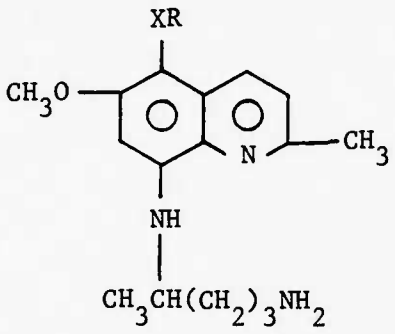
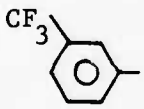
No.	R	X	Cures (C), Toxic Deaths (T) or △MST Dose, mg/kg							
			5	10	20	40	80	160	320	640
BL 20738		S			0.0	0.8	0.6	0.2	3.8	2T
BL 28449	$CH_3(CH_2)_5$	S			2.1	5.9	1C	3C	5C	5C
BK 42882	$CH_3(CH_2)_5$	O		2.7	6.0	1C	11.4	3C	3T	3T

TABLE IX

COMPARISON OF 5-PHENYLTHIO, 5-ALKYLTHIO AND 5-ALKOXYPRIMAQUINES RADICAL CURATIVE ANTIMALARIAL ACTIVITY (P. cynomolgi, Rhesus)



No.	R	X	Cures /No. of Animals Dose, mg/kg				
			0.1	0.316	1.0	3.16	10.0
BL 20738		S			Pending		
BL 28449	$CH_3(CH_2)_5$	S		0/3	1/3	2/2	
BL 42882	$CH_3(CH_2)_5$	O	0/2	1/1	0/1		

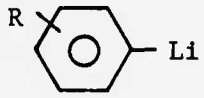
4-METHYL-5-[5-(R-PHENYL)PENTOXY] PRIMAQUINES

Synthesis of the target compounds (57-62, 64) has been effected as outlined in Scheme 1. Early attempts to make the alkylating agents, 19 and 26 were unsuccessful; 26 was subsequently prepared using the alternate route shown in Scheme 2. Preparation of the target, 63, has reached stage 36.

The alkylating agents (20-27) were made via an adaptation of the method of Klayman et al.[1] The remaining steps in Scheme 1 were adaptations of those described earlier by Nodiff et al.[2,3]

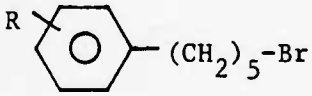
Scheme 1

1 R = 2-Cl
2 R = 2-CF_3
3 R = 4-F
4 R = 4-Cl
5 R = 4-CF_3
6 R = 4-CH_3
7 R = 4-CH_3O
8 R = 4-CH_3SO_2
9 R = 4-Cl, 3-CF_3



10 R = 2-Cl
11 R = 2-CF_3
12 R = 4-F
13 R = 4-Cl
14 R = 4-CF_3
15 R = 4-CH_3
16 R = 4-CH_3O
17 R = 4-CH_3SO_2
18 R = 4-Cl, 3-CF_3

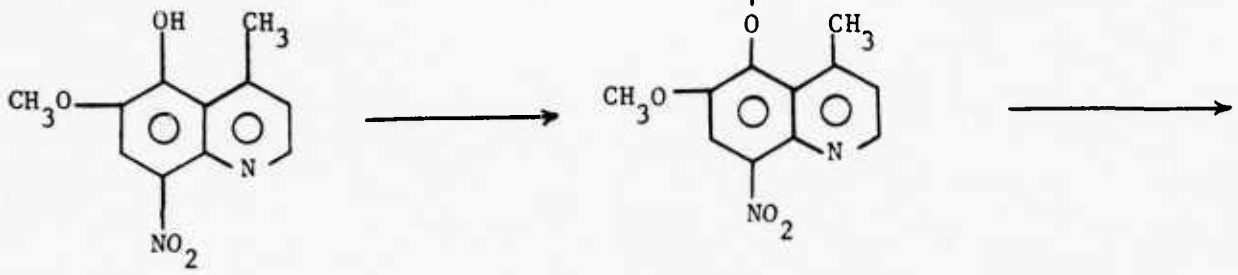
$Br(CH_2)_5Br$ ⟶



+

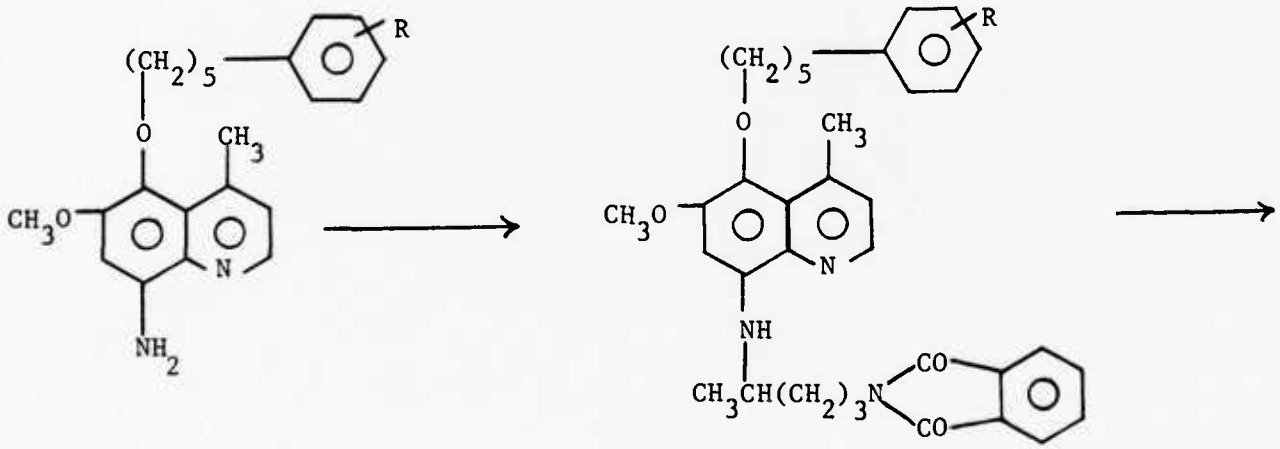
19 R = 2-Cl
20 R = 2-CF_3
21 R = 4-F
22 R = 4-Cl
23 R = 4-CF_3
24 R = 4-CH_3
25 R = 4-CH_3O
26 R = 4-CH_3SO_2
27 R = 4-Cl, 3-CF_3

Scheme 1, Continued



28

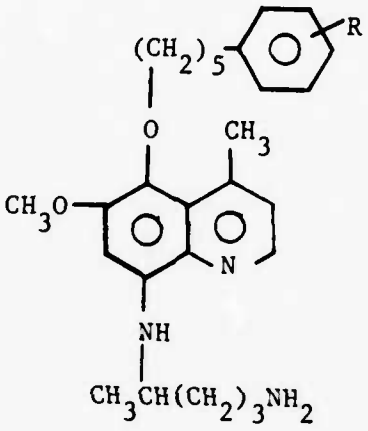
29 R = 2-Cl
30 R = 2-CF_3
31 R = 4-F
32 R = 4-Cl
33 R = 4-CF_3
34 R = 4-CH_3
35 R = 4-CH_3O
36 R = 4-CH_3SO_2
37 R = 4-Cl, 3-CF_3



38 R = 2-Cl
39 R = 2-CF_3
40 R = 4-F
41 R = 4-Cl
42 R = 4-CF_3
43 R = 4-CH_3
44 R = 4-CH_3O
45 R = 4-CH_3SO_2
46 R = 4-Cl, 3-CF_3

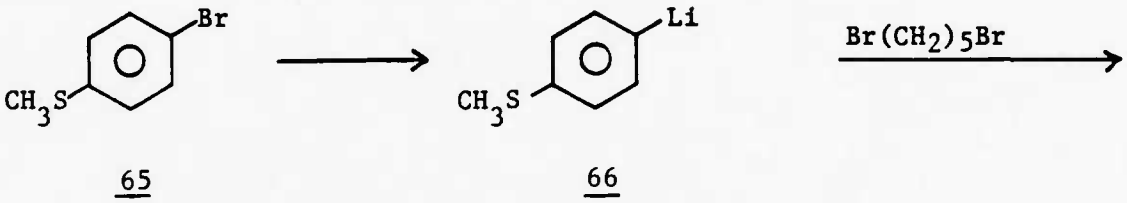
47 R = 2-Cl
48 R = 2-CF_3
49 R = 4-F
50 R = 4-Cl
51 R = 4-CF_3
52 R = 4-CH_3
53 R = 4-CH_3O
54 R = 4-CH_3SO_2
55 R = 4-Cl, 3-CF_3

Scheme 1, Continued

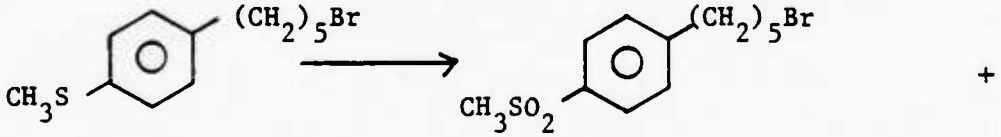


56 R = 2-Cl
57 R = 2-CF_3
58 R = 4-F
59 R = 4-Cl
60 R = 4-CF_3
61 R = 4-CH_3
62 R = 4-CH_3O
63 R = 4-CH_3SO_2
64 R = 4-Cl, 3-CF_3

Scheme 2



65 66



67 26

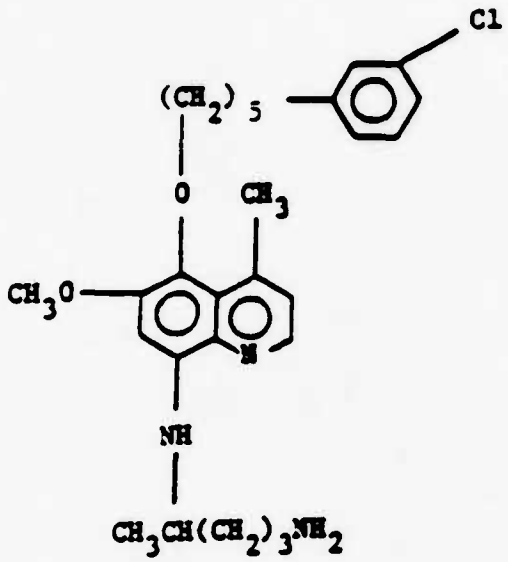
4-METHYL-5-[5-(3-CHLOROPHENYL)PENTOXY]PRIMAQUINE

We had received two disparate sets of blood schizonticidal data (Table VI) for the title compound (BL 50076).

TABLE X

BLOOD SCHIZONTICIDAL ANTIMALARIAL ACTIVITY

(P. berghei, Mouse)



BL 50076

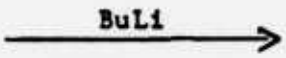
Date	GRP	TST	Cures (C), Toxic Deaths (T) or ΔMST Dose, mg/kg									
			0.04	0.08	0.16	0.32	0.63	1.25	2.5	5	10	20
88019	G70	3						5.2	7.0	7.8	4C	4C
88040	G73	3	4.8	5.4	7.6	3C	5C	5C				

The data obtained on date, 88019, indicated no cures below 10 mg/kg. However, the data for date, 88040 showed multiple cures at the extraordinarily low dose, 0.32 mg/kg. In order to permit confirmatory screening, we prepared an additional quantity of the target compound following Scheme 3.

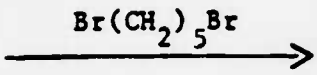
Contract No. DAMD17-88-C-8106

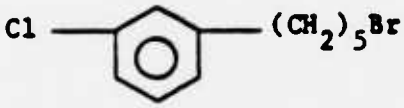
Scheme 3

68



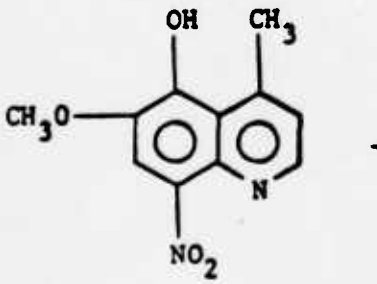
69



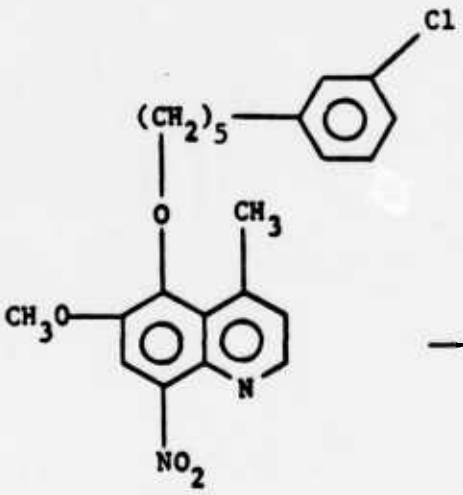


+

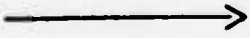
70



28

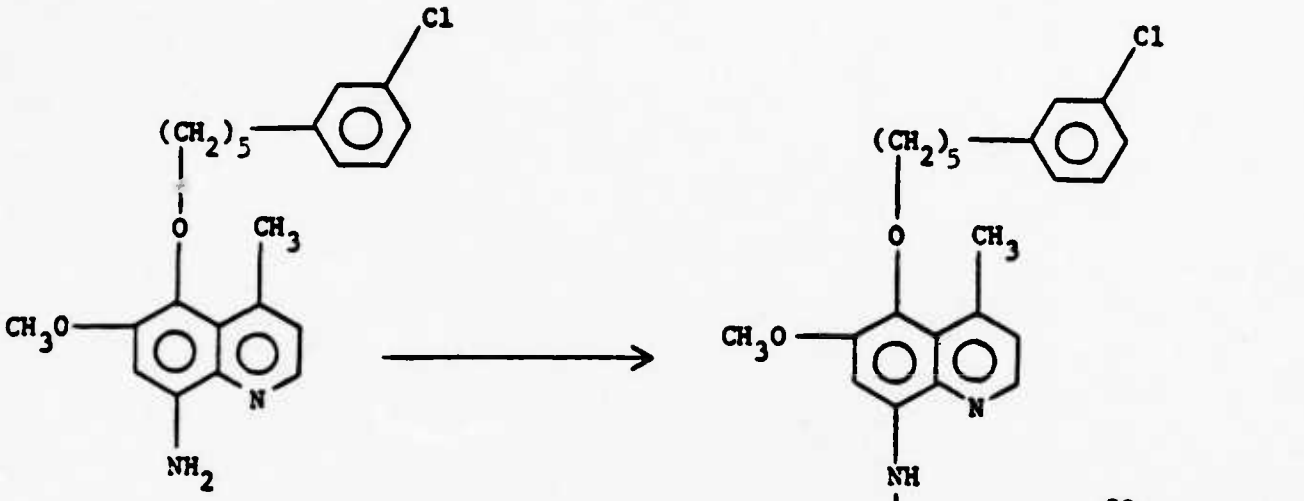


71



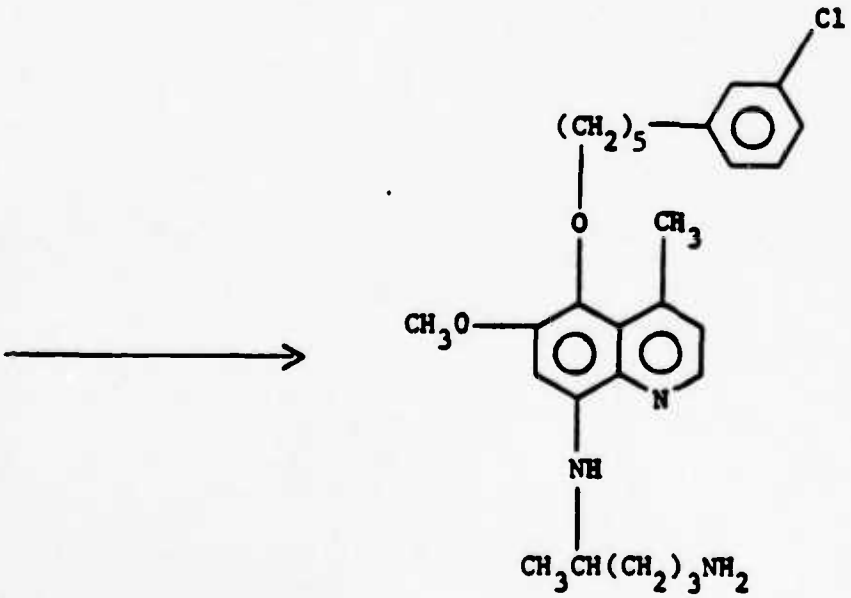
Contract No. DAMD17-88-C-8106

Scheme 3 - Continued



72

73

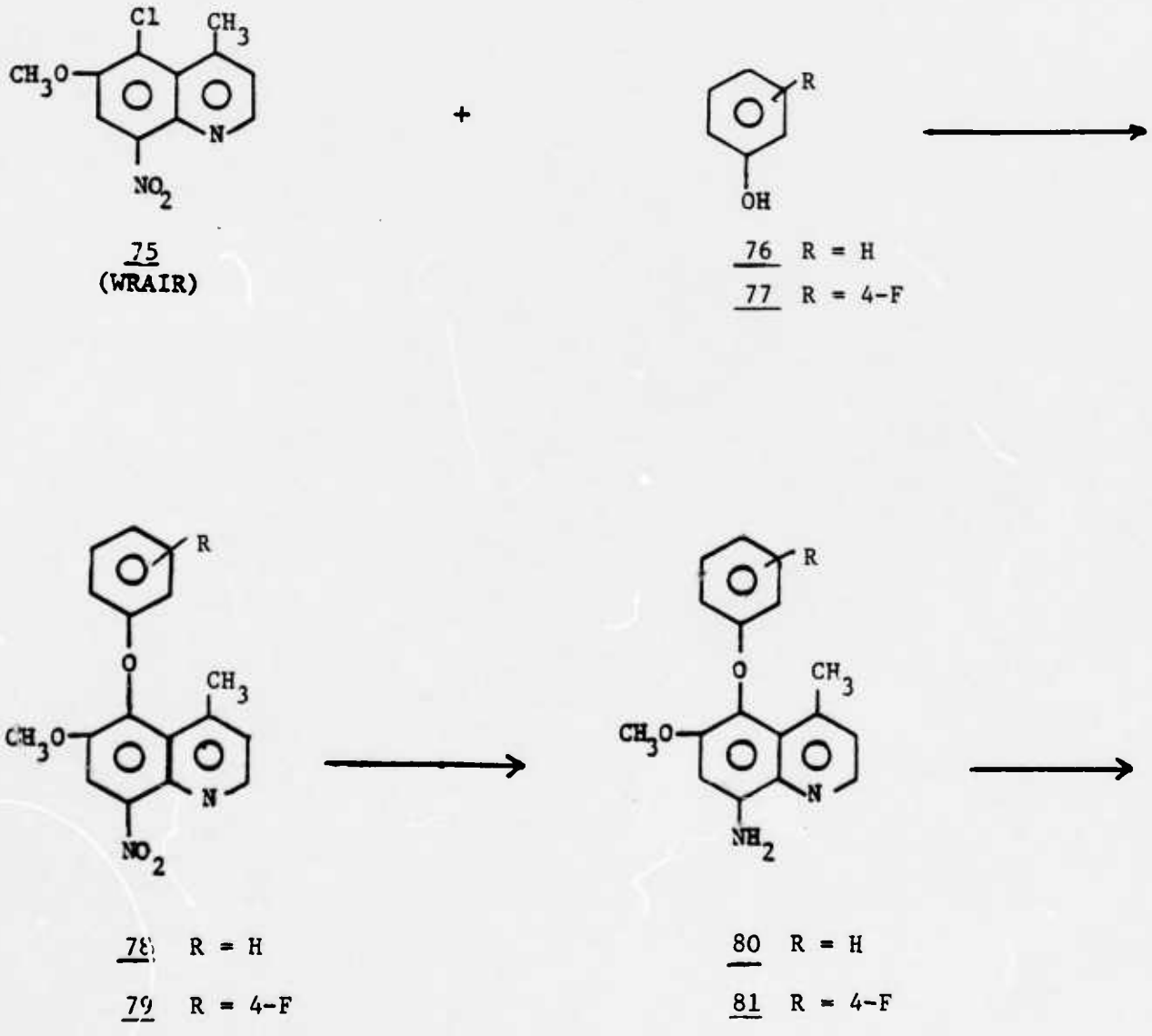


74

2-METHOXY-4-METHYL-5-(R-PHENOXY)PRIMAQUINES

Synthesis of the title compounds has been initiated according to Scheme 4. Preparation of the targets 94 and 95 has reached the penultimate stages, 92 and 93, respectively.

Scheme 4



75 (WRAIR)

76 R = H

77 R = 4-F

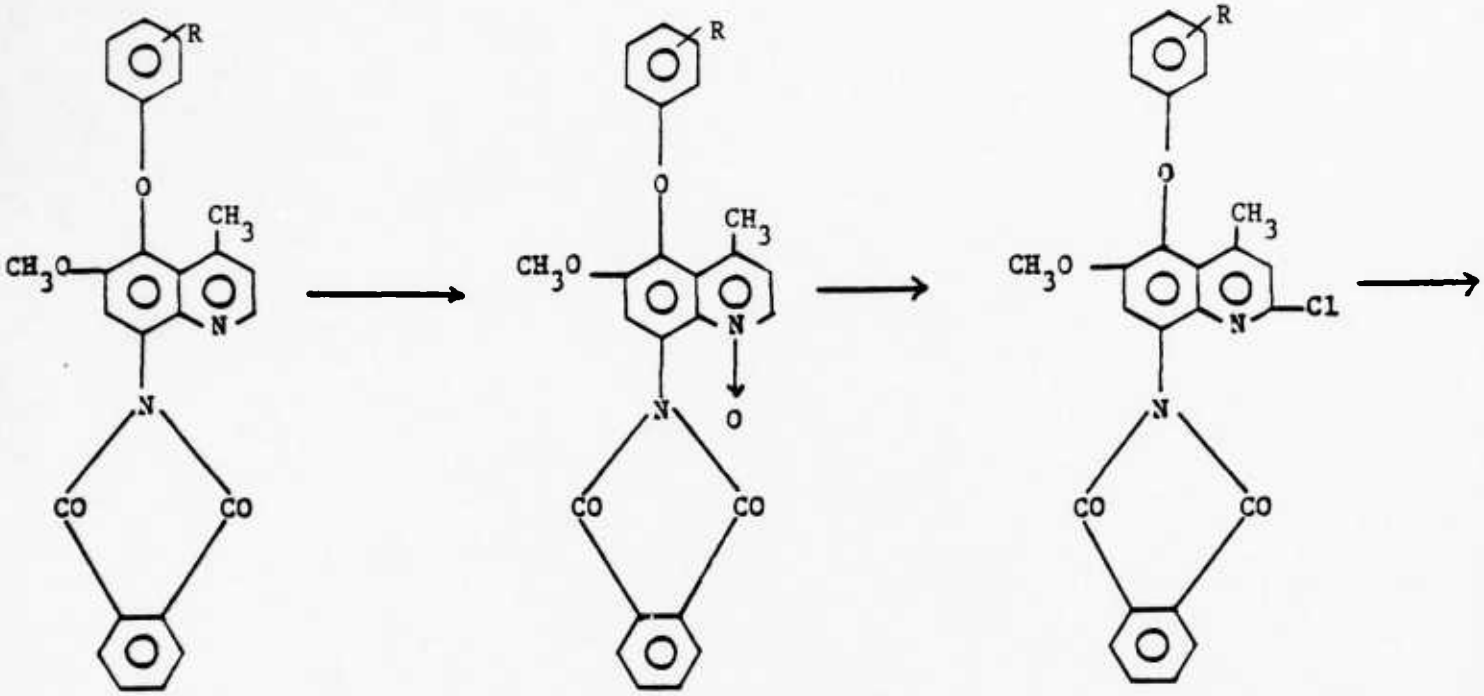
78 R = H

79 R = 4-F

80 R = H

81 R = 4-F

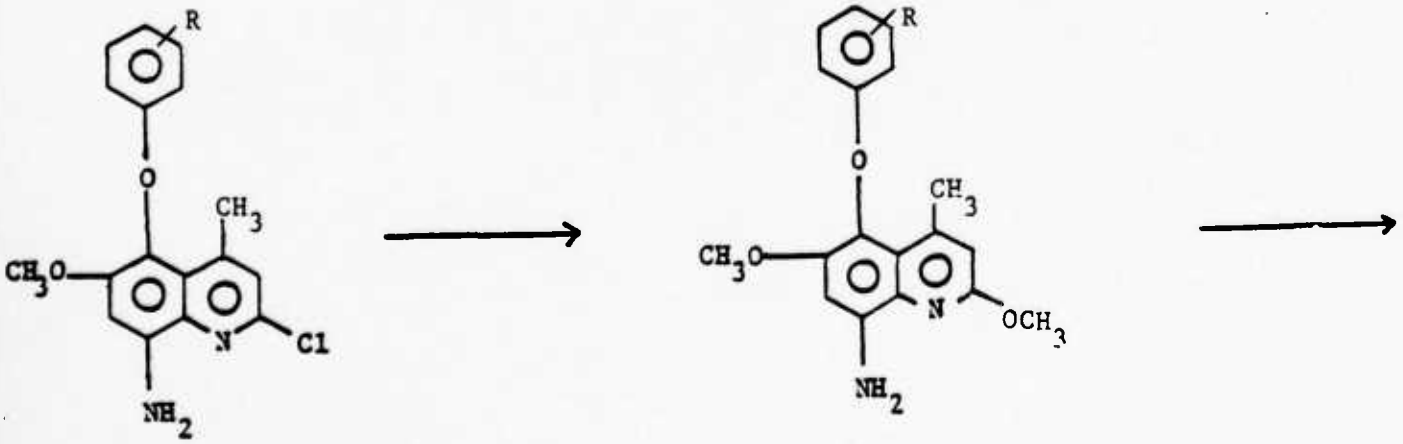
Scheme 4, Continued



82 R = H
83 R = 4-F

84 R = H
85 R = 4-F

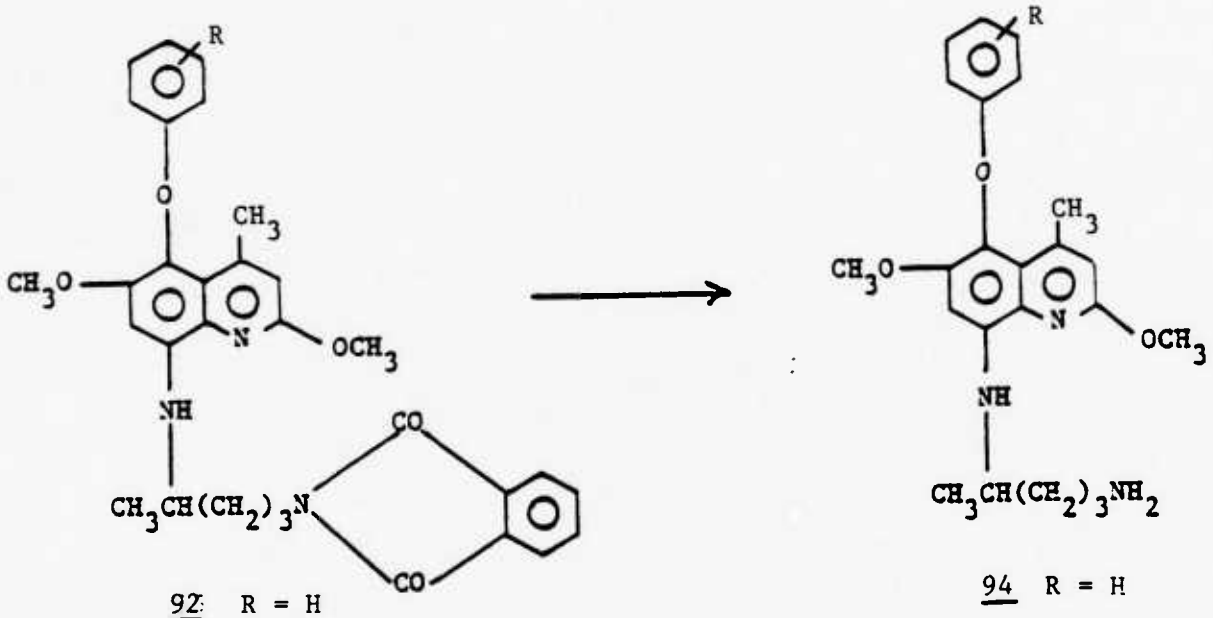
86 R = H
87 R = 4-F



88 R = H
89 R = 4-F

90 R = H
91 R = 4-F

Scheme 4, Continued



92 R = H

93 R = 4-F

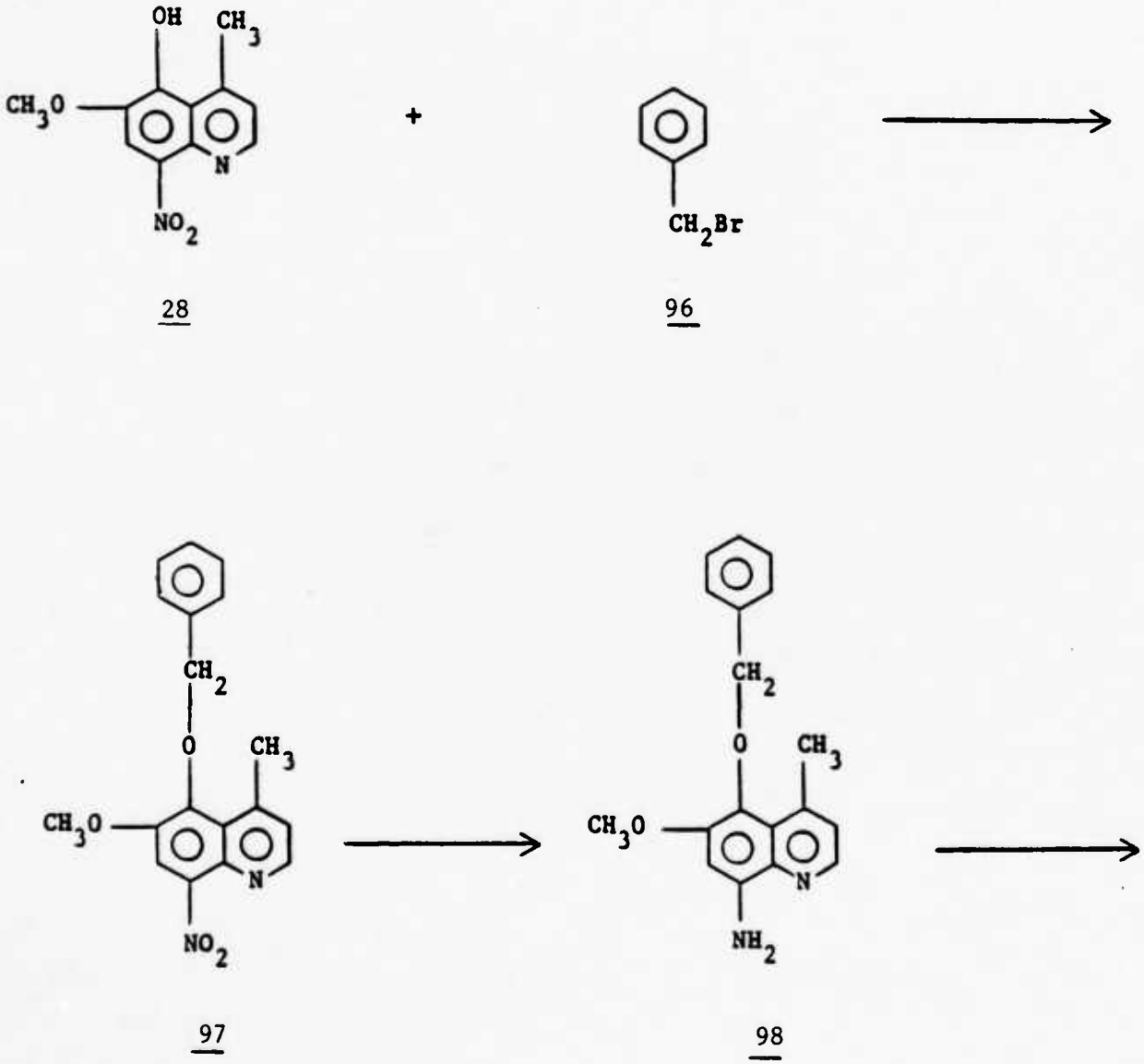
94 R = H

95 R = 4-F

5-BENZYLOXY-2-METHOXY-4-METHYLPRIMAQUINE

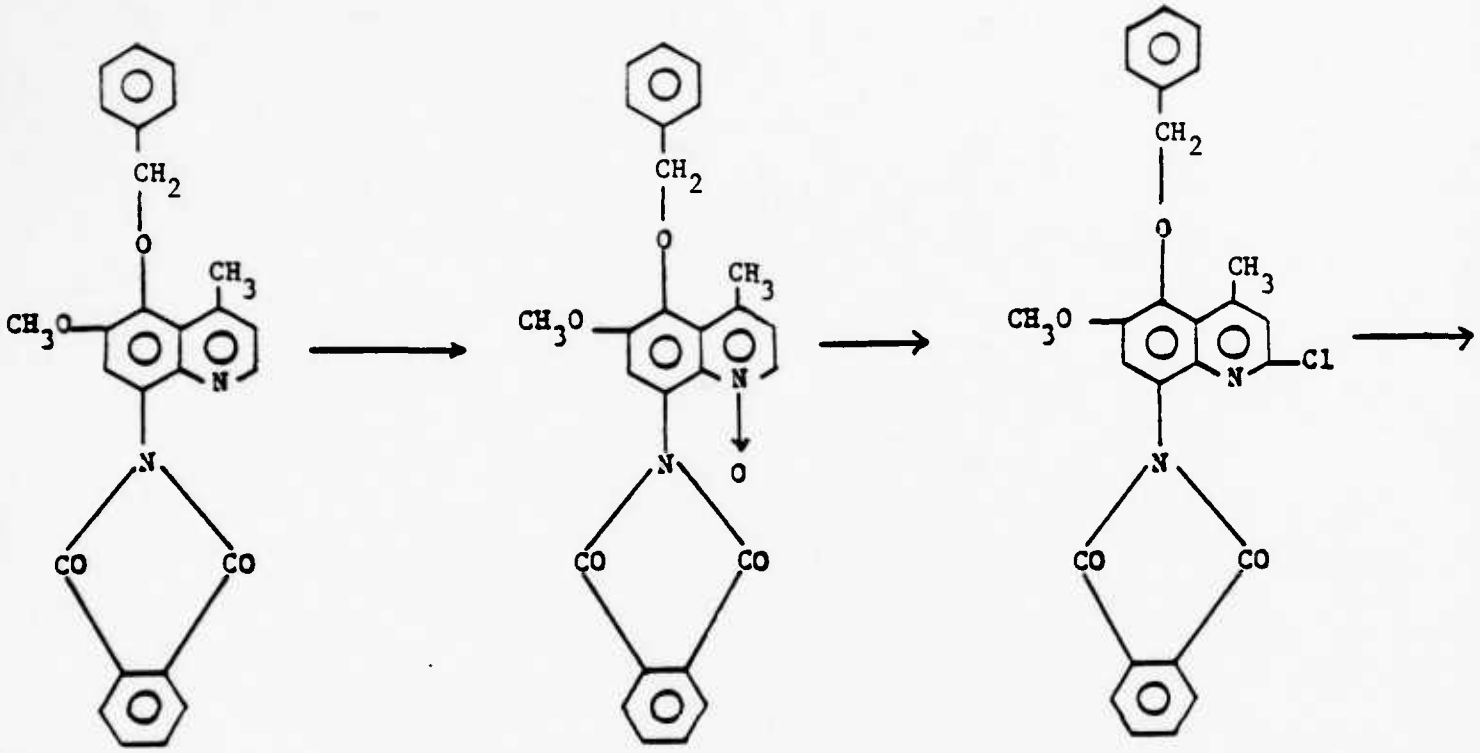
The 8-phthalimidoquinoline (99) has been prepared as an intermediate in the synthesis of the title compound (Scheme 5).

Scheme 5

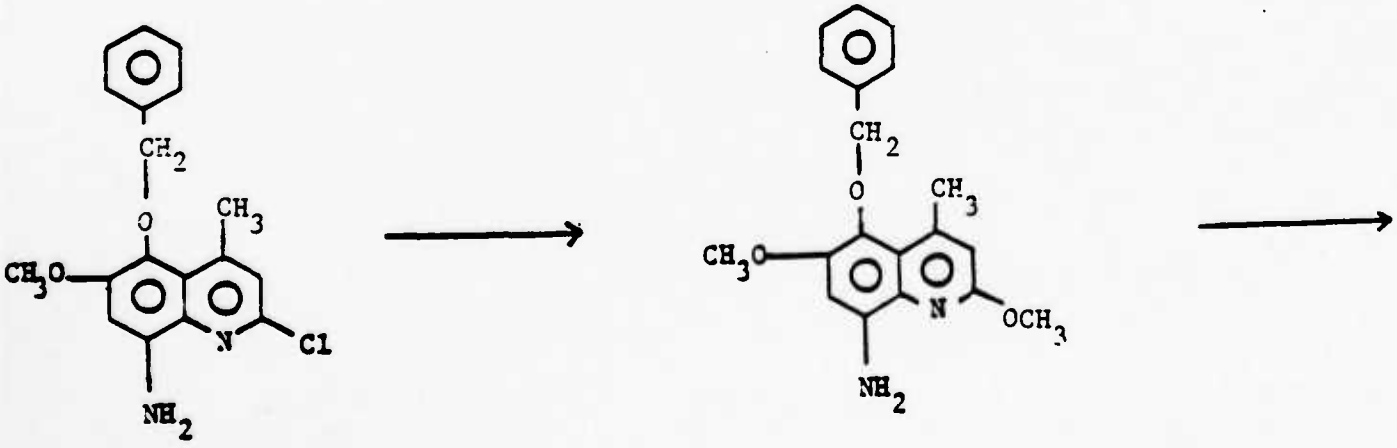


28 96 97 98

Scheme 5, Continued

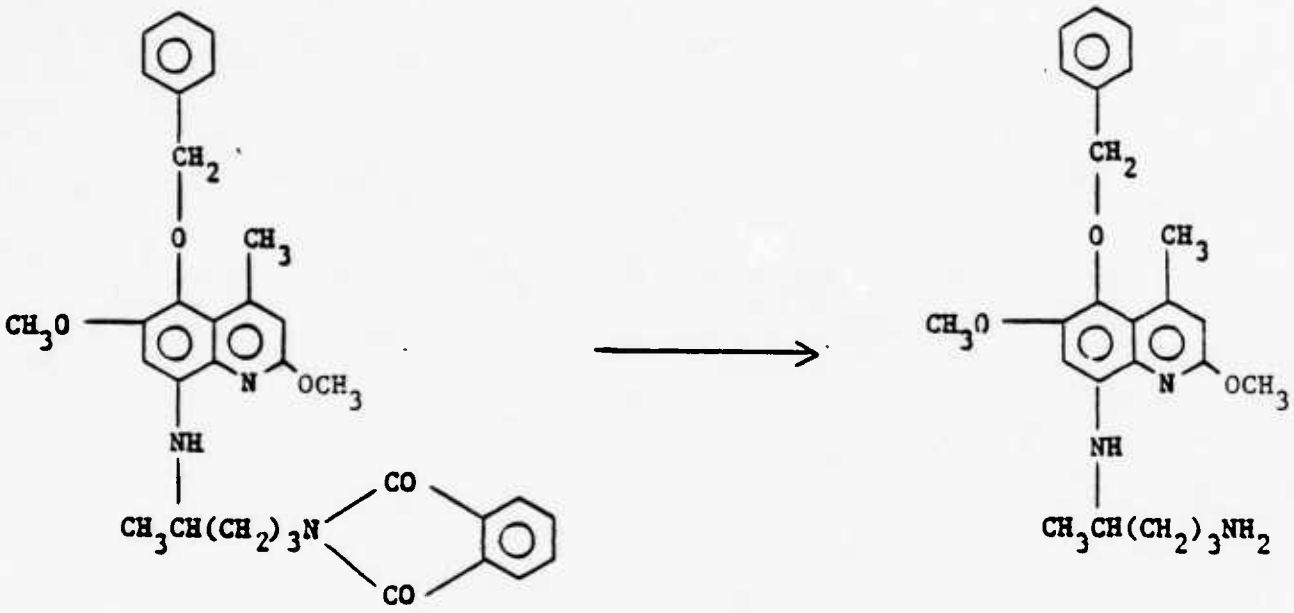


99 100 101



102 103

Scheme 5, Continued

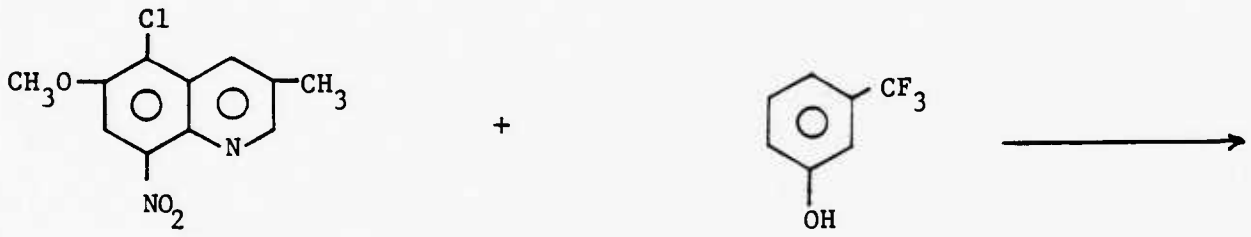


104 105

2-METHOXY-3-METHYL-5-(3-TRIFLUOROMETHYLPHENOXY)PRIMAQUINE

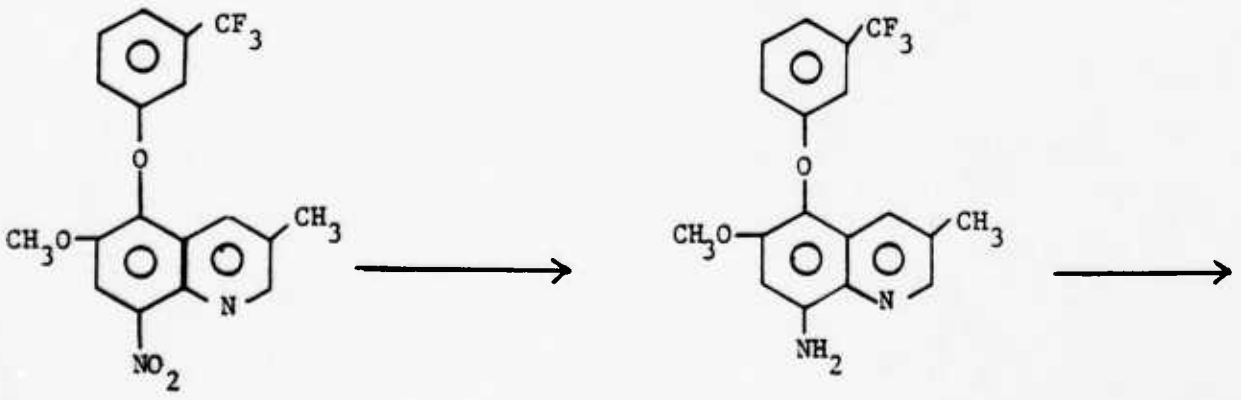
The reaction between 106 and 107 is in progress.

Scheme 6



106
(WRAIR)

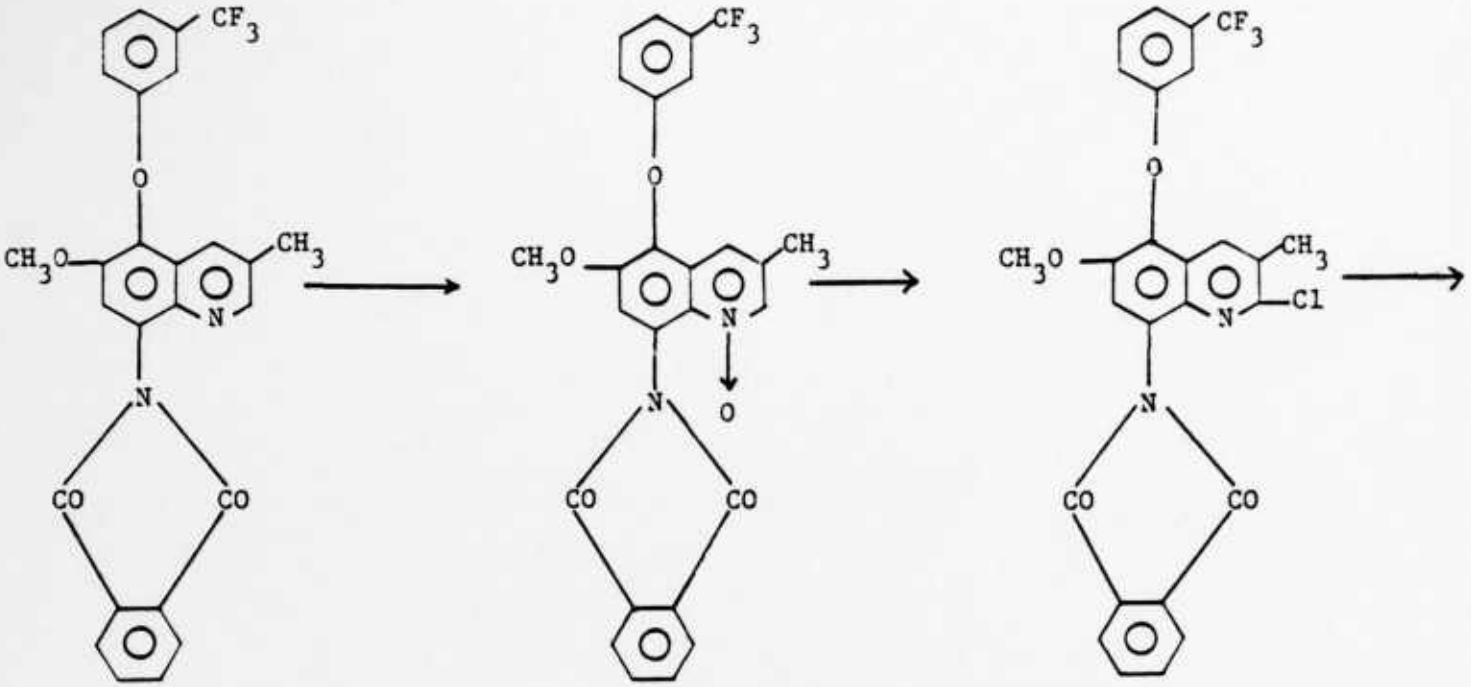
107



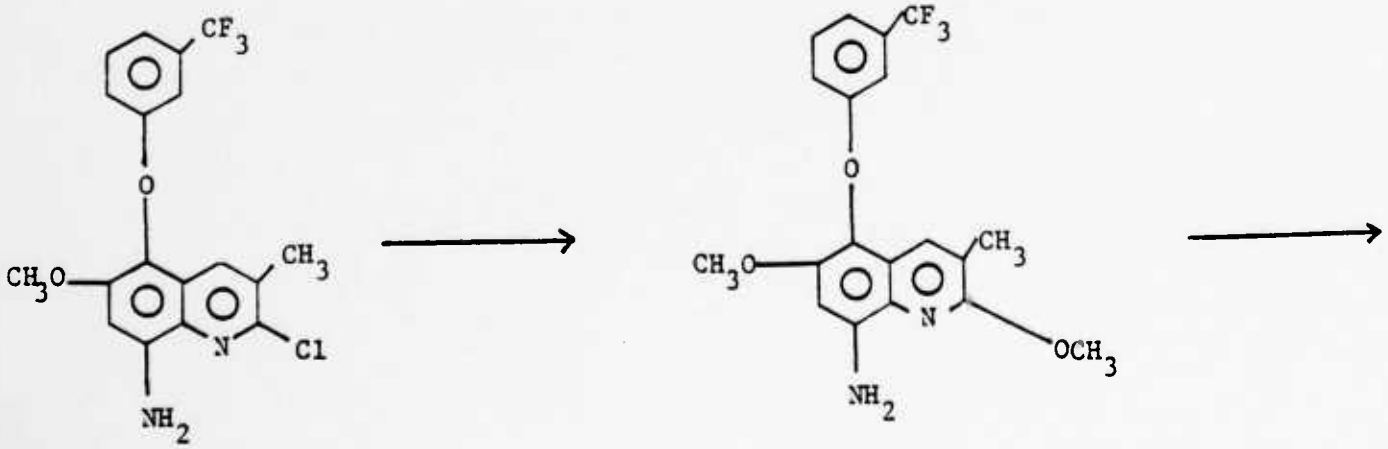
108

109

Scheme 6, Continued

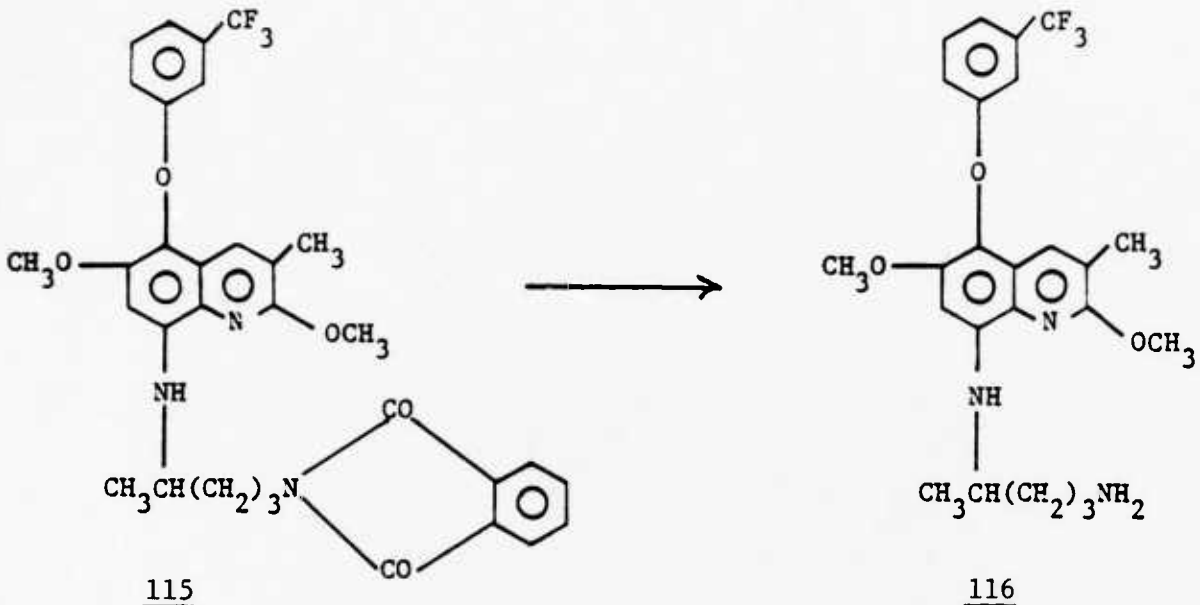


110 111 112



113 114

Scheme 6, Continued

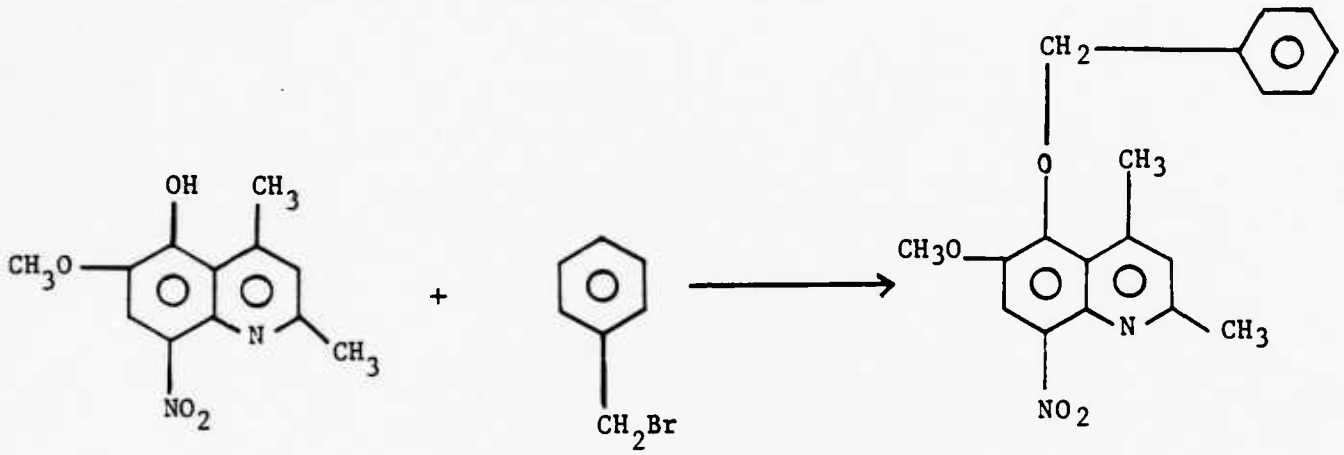


115 116

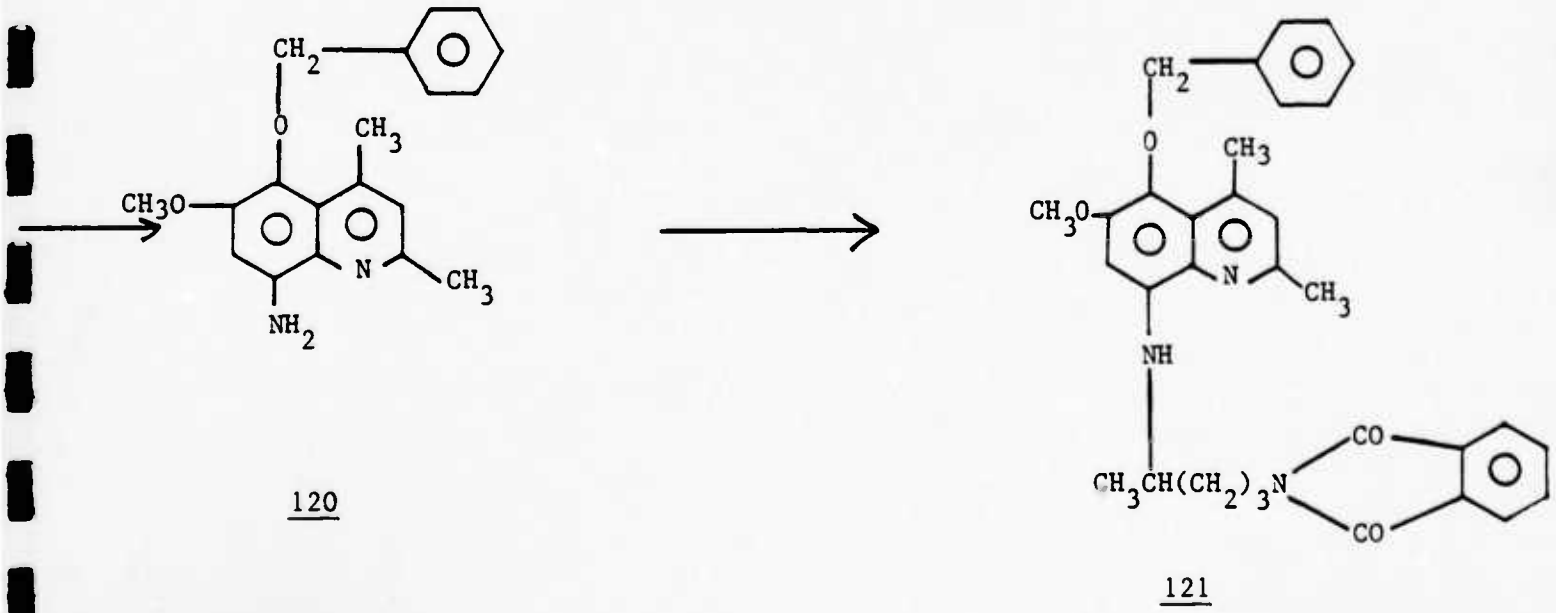
2,4-DIMETHYL-5-BENZYLOXYPRIMAQUINE

This synthesis has been carried to Stage 119.

Scheme 7

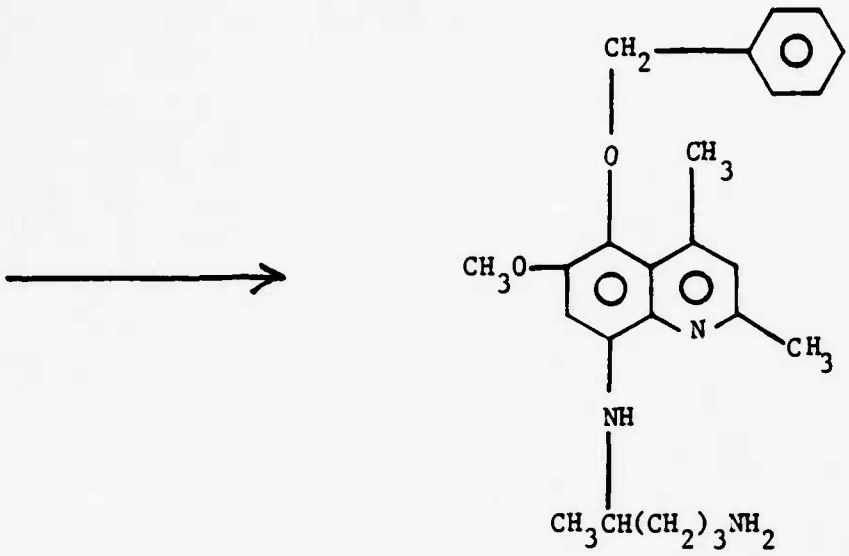


117 (WRAIR) 118 119



120 121

Scheme 7, Continued



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EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Delaware. Infrared spectra were taken on a Perkin-Elmer Model 1420 Spectrophotometer.

1-Bromo-5-(2-trifluoromethylphenyl)pentane (20)

To a stirred mixture of 2 (Aldrich; 22.5 g, 0.1 mol), THF (140 ml) and hexane (60 ml), under N_2, at an internal temperature of -76°C, was slowly added (25 minutes), 40 ml (0.1 mol) of a 2.5 M solution of BuLi in hexane (Aldrich); The internal temperature remained below -70°C during addition. The dark brown mixture was stirred at -75°C for 30 minutes and treated with 1,5-dibromopentane (23.0 g, 0.1 mol) at a rate which kept the internal temperature below -70°C. The mixture was allowed to rise to room temperature during 1 h, stirred for an additional hour, cooled to 0°C and slowly added to water-ice (400 ml). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organic solutions were washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4) and evaporated to a black oil. Fractional distillation gave 13.24g (45%) of 20 as a colorless oil, bp 90-92°C/0.9 mm; n_D^{25} 1.4855.

Anal. Calcd. for $C_{12}H_{14}BrF_3$: C, 48.83; H, 4.78.
Found: C, 48.91; H, 4.83

6-Methoxy-4-methyl-8-nitro-5-[5-(2-trifluoromethylphenyl)pentoxy]quinoline (30)

To a stirred mixture of 28 (WRAIR)(9.5 g, 0.041 mol), 20 (12.0 g, 0.041 mol) and HMPA (30 ml), at 110-115°C, was added dropwise, during 75 min, a solution of Et_3N (5 ml) and propylene oxide (20 ml). Heating was continued for 6 h at 125-130°C. The mixture was allowed to cool and exhaustively extracted with 400 ml of a 1:1 solution of pet ether (35-60°C) and Et_2O.

The combined extracts were washed with 10% NaOH (3 x 100 ml), H_2O (3 x 100 ml), dried (Na_2SO_4), treated with carbon (Darco) and concentrated to a black oil. The oil was pumped for 2 h at room temperature and 0.5 mm and triturated with hexane (15 ml) until solidification occurred. The solid was filtered, washed with hexane (30 ml) and air-dried to give 6.5 g (36%) of 30 as a yellow solid, mp 56-57°C, which was used without further purification. An aliquot was crystallized twice from hexane to give the analytical sample, mp 60-61°C.

Anal. Calcd. for $C_{23}H_{23}F_3N_2O_4$: C, 61.60; H, 5.17; N, 6.25.
Found: C, 61.86; H, 5.38; N, 6.45.

8-Amino-6-methoxy-4-methyl-5-[5-(2-trifluoromethylphenyl)pentoxy]quinoline (39)

A stirred mixture of 30 (6.0 g, 0.0134 mol), Fe - filings (7.5 g), H_2O (100 ml), AcOH (1.5 ml) and Bu_2O (15 ml) was heated at 95-100°C for 2 h, allowed to cool and exhaustively extracted with Et_2O (total, 400 ml). The extract was washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4), treated with carbon (Darco) and evaporated to a dark yellow oil. After being pumped for 4 h at 0.5 mm, the oil was triturated with hexane (10 ml) at 0°C until a yellow solid appeared; yield 4.28 g (76%), mp 58-59°C. Recrystallization of an aliquot from hexane (2X) gave the analytical sample as yellow crystals, mp 59-60°C.

Anal. Calcd. for $C_{23}H_{25}F_3N_2O_2$: C, 66.01; H, 6.02; N, 6.70.
Found: C, 66.19; H, 6.09; N, 6.46.

6-Methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)-5-[5-(2-trifluoromethylphenyl)pentoxy]quinoline (48)

A stirred mixture of 39 (4.0 g, 0.0096 mol) and 4-bromo-1-phthalimidopentane (BPP) (5.66g, 0.019 mol) was heated at 110-115°C while Et_3N (2.5 ml) was slowly added during 45 min. After 2 h at 110-115°C, more BPP (3.3 g) and Et_3N (0.75 ml during 10 min) were added. Heating was continued for 2 h and additional BPP (1.9 g) was introduced.

After 2 h at 120-125°C, final quantities of BPP (1.4g) and Et_3N (0.5 ml) were added and the mixture was heated at 120-125°C for 2 h. On cooling, the mixture was applied to a silica gel column and eluted with $CHCl_3$. Concentration of the eluates gave 4.86 g (80%) of 48 as a dark yellow oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5-[5-(2-trifluoromethylphenyl)pentoxy]quinoline Fumarate (57)

A stirred solution of 48 (4.86 g, 0.0077 mol), $CHCl_3$ (50 ml), EtOH (100 ml) and 95% NH_2NH_2 (9 ml) was heated under reflux for 3 h, allowed to cool, concentrated and extracted with Et_2O. The extract was washed with 20% KOH (3 x 75 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and evaporated to a yellow oil. The oil was dissolved in CH_3CN (30 ml) and treated with 40 ml of a boiling solution of fumaric acid (0.89g) in MeOH-CH_3CN (1:4 v/v). The resulting precipitate was washed with CH_3CN (3 x 15 ml), crystallized from CH_3CN and vacuum-dried to give 2.37 g (50%) of 57 as a yellow solid, mp 154-155°C (decomp).
Anal. Calcd. for $C_{32}H_{40}F_3N_3O_6$: C, 62.02; H, 6.51; N, 6.78.
Found: C, 62.16, H, 6.62; N, 6.50

1-Bromo-5-(4-fluorophenyl)pentane (21)

To a stirred mixture of 4-fluorobromobenzene (3) (Aldrich; 35.0 g, 0.20 mol) in anhydrous Et_2O (250 ml), under N_2, at -40°C, was added dropwise during 30 min., 20 ml of a 10 M solution of BuLi in hexane (Aldrich) diluted with an additional 20 ml of dry hexane. The temperature rose to -30°C during addition and stirring was continued at -30°C for 30 more minutes. The mixture was treated with 1,5-dibromopentane (Aldrich; 46.0 g, 0.20 mol), dropwise, during 10 min., allowed to warm to -10°C, stirred for 20 min., diluted with THF (150 ml), during 30 min., stirred at -10°C for 30 min., and slowly brought to room temperature. The mixture was slowly poured over crushed dry ice (200 g) and the resulting mixture was carefully added to cold H_2O (500 ml). The aqueous layer was extracted with Et_2O (3 x 200 ml) and the combined extracts and organic layer were washed with 10% Na_2CO_3 (3 x 100 ml), saturated NaCl solution (2 x 200 ml), dried (Na_2SO_4) and concentrated to a pale yellow oil. Fractional distillation gave 18.76 g (38%) of 21 as an oil, bp 128-129°C/3.5 mm, which was used without further purification.

5-[5-(4-Fluorophenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (31)

To a stirred mixture of 28 (WRAIR; 6.03 g, 0.026 mol), 21 (6.32 g, 0.026 mol) and HMPA (20 ml), at 120-130°C, was added, dropwise, during 90 min., a solution of propylene oxide (20 ml) and Et_3N (5 ml). The mixture was heated for an additional 5 h, allowed to cool, extracted with Et_2O (300 ml) and Me_2CO to leave 2.26 g of starting material 28. The ether extract was washed with 5% NaOH (3 x 100 ml), H_2O (3 x 100 ml), dried (Na_2SO_4) and evaporated, in vacuo, to a black oil. The oil was placed on a silica gel column and eluted with $CHCl_3$. Concentration of the eluates gave a yellow oil which solidified on standing in the refrigerator (4.1 g, 48%). Crystallization from hexane provided an analytical sample as yellow crystals, m.p. 64-65°C.

Anal. Calcd. for $C_{22}H_{23}FN_2O_4$; C, 66.32; H, 5.82; N, 7.03
Found: C, 66.02; H, 5.85; N, 6.76

8-Amino-5-[5-(4-fluorophenyl)pentoxy]-6-methoxy-4-methylquinoline (40)

A stirred mixture of 31 (7.28 g, 0.018 mol), Fe filings (6 g), H_2O (100 ml), Bu_2O (12 ml) and HOAc (1.5 ml) was heated at 105-110° for 1.5 h, allowed to cool and filtered. The solid and the filtrate were extracted with Et_2O and the combined extracts (400 ml) were washed with saturated NaCl solution (3 x 100 ml), dried (Na_2SO_4) and concentrated to a dark oil. The oil was combined with identical material from a similar run which started with 2.5 g (0.0063 mol) of 31. The combined oils were placed on a silica gel column and eluted with $CHCl_3$. Concentration of the eluates gave 6.33 g (70%) of 40 as an oil which solidified on standing. This material was used without further purification.

5-[5-(4-Fluorophenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutyl-amino)quinoline (49)

A stirred mixture of 40 (4.18 g, 0.0113 mol) and 4-bromo-1-phthalimidopentane (BPP) (6.72 g, 0.0226 mol) was heated at 125-130°C while Et_3N (3 ml) was added in small portions during 30 min. After two more hours of heating, additional quantities of BPP (3.36 g) and Et_3N (1 ml) were introduced during 15 min. Heating was continued for 3 h, the mixture was allowed to cool, placed on a silica gel column and eluted with $CHCl_3$. The eluates were concentrated to give 6.34g (96%) of 49 as a yellow-orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(4-fluorophenyl)pentoxy]-6-methoxy-4-methyl-quinoline Fumarate (58)

A stirred mixture of 49 (3.68 g, 0.0063 mol), $CHCl_3$ (25 ml), EtOH (50 ml) and 95% NH_2NH_2 (10 ml) was heated at 85-90°C for 1.5 h, cooled and filtered. The solid was washed with a small amount of EtOH and the combined filtrate and washings were concentrated to an orange oil. This material was dissolved in Et_2O (200 ml), washed with 25% KOH (3 x 75 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and concentrated to a dark yellow oil. The oil was dissolved in CH_3CN (15 ml) and slowly treated with fumaric acid (0.6 g) in 30 ml of a boiling solution of MeOH and CH_3CN (1:4). On standing overnight at room temperature, a solid precipitated which was crystallized from CH_3CN to give 1.8 g (50%) of 58 as a yellow solid, m.p. 148-150°C (decomp).

Anal. Calcd. for $C_{31}H_{40}FN_3O_6$: C, 65.36; H, 7.08; N, 7.38.
Found: C, 64.98; H, 7.16; N, 7.14

1-Bromo-5-(4-chlorophenyl)pentane (22)

To a stirred solution of 4 (Aldrich; 39 g, 0.2 mol) in anhydrous Et_2O (300 ml), at -25°C, under N_2, was slowly added, during 20 min, a solution of 10 M BuLi in hexane (Aldrich, 20 ml, 0.2 mol) diluted with an additional 10 ml of hexane. The yellow emulsion was stirred at -15°C for 0.5 h, cooled to -35°C, treated with 1,5-dibromopentane (46 g, 0.2 mol) during 10 min and then with THF (200 ml) during 30 min.

The resulting white suspension was stirred at -30°C to -15°C for 1 h, allowed to warm to room temperature, slowly poured over dry-ice (200 g) and the yellow solution was added to H_2O (500 ml). The aqueous layer was separated and extracted with Et_2O (4 x 150 ml). The organic layer and the ethereal extracts were combined, washed with 10% Na_2CO_3 and saturated brine, dried (Na_2SO_4) and concentrated to a yellow oil. Fractional distillation gave 22.8 g (44%) of 22, bp 115-116°C/0.5 mm; n_D^{23} 1.5430. This material was used without further purification.

5-[5-(4-Chlorophenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (32)

To a stirred mixture of 28 (WRAIR, 11.96 g, 0.05 mol), 22 (13.37 g, 0.05 mol) and HMPA (50 ml), at 115-120°C, was added dropwise, during 90 min, a solution of propylene oxide (24 ml) and Et_3N (8 ml). The mixture was heated at 115-120°C for 6h, allowed to cool and extracted with a 1:1 mixture (400 ml) of pet ether (20-40°C) and Et_2O. The extract was washed with 10% NaOH (3 x 75 ml), H_2O (2 x 75 ml), dried (Na_2SO_4) and treated with carbon (Darco G-60). Solvent concentration gave a yellow solid which was filtered, washed with pet ether (20-40°C) and air-dried to give 8.10 g (38%) of 32 which was used without further purification. Crystallization of an aliquot from hexane gave an analytical sample as yellow crystals, mp 77-78°C.

Anal. Calcd. for $C_{22}H_{23}ClN_2O_4$: C, 63.69; H, 5.59; N, 6.75.
Found: C, 63.74; H, 5.83; N, 6.68

8-Amino-5-[5-(4-chlorophenyl)pentoxy]-6-methoxy-4-methylquinoline (41)

A stirred mixture of 32 (6.46 g, 0.016 mol), Fe-filings (8 g), Bu_2O (30 ml), H_2O (100 ml) and HOAc (1.5 ml) was heated at 105-110°C for 3h, allowed to cool and filtered. The filtrate and the residue were extracted with Et_2O (300 ml). The combined extracts were washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4), treated with carbon (Darco) and concentrated to a small volume which on cooling and scratching gave a yellow solid. Filtration, washing with hexane and air-drying gave 3.71 g (62%) of 41 as yellow crystals, m.p. 69-71°C. The mother liquor was diluted w[illegible]hexane (50 ml) and cooled overnight to give another 1.04 g (17%) of 41. [illegible]ombin[illegible]mate[illegible] was used without further purification.

5-[5-(4-Chlorophenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (50)

A stirred mixture of 41 (3.27 g, 0.009 mol) and 4-bromo-1-phthalimidopentane (BPP) (5.23 g, 0.018 mol) was heated at 120-125°C while Et_3N (3 ml) was slowly added during 30 min. After 3.5h at 120-125°C, more BPP (3.42 g, 0.012 mol) and Et_3N (2 ml during 30 min.) were added and heating was continued for 5h. On cooling, the mixture was exhaustively extracted with Et_2O (300 ml). The extract was washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4) and concentrated to a dark oil. The oil was pumped at 1.8 mm Hg for 2h, applied to a silica gel column and eluted with $CHCl_3$. Concentration of the product eluates gave 4.53 g (89%) of 50 as an orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(4-chlorophenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (59)

A stirred solution of 50 (4.53 g, 0.0076 mol), $CHCl_3$ (25 ml), EtOH (50 ml) and 95% NH_2NH_2 (3 ml) was heated under reflux for 2h, allowed to cool and filtered. The white residue was washed with EtOH and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et_2O (100 ml), and the solution was washed with 20% KOH solution (3 x 50 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and concentrated to a viscous dark yellow oil (2.88 g, 81%). The oil was dissolved in CH_3CN (25 ml) and slowly treated with a hot solution of fumaric acid (0.71 g) in CH_3OH-CH_3CN (1:4 V/V, 35 ml). The resulting yellow solid was separated by decantation, washed with CH_3CN (3 x 20 ml), recrystallized from CH_3CN and vacuum dried (1.2 mm Hg, 20°C, 2h) to give 2.60 g (59%) of 59 as a yellow solid, mp 152-153°C (decomp.).

Anal. Calcd. for $C_{31}H_{40}ClN_3O_6$: C, 63.52; H, 6.88; N, 7.17
Found: C, 63.63; H, 6.84; N, 7.13

1-Bromo-5-(4-trifluoromethylphenyl)pentane (23)

This compound was prepared in a manner identical with that described for the 2-isomer (20). The yield of 23, from 22.5 g (0.1 mol) of 5, was 11.08 g (38%); bp 94-96°C/0.8 mm; n_D^{23} 1.4805

6-Methoxy-4-methyl-8-nitro-5-[5-(4-trifluoromethylphenyl)pentoxy]quinoline (33)

This synthesis was identical with that described for the 2-isomer (30). The yield of 33, from 8.78 g (0.0375 mol) of 28, was 8.95 g (53%) as a yellow solid, mp 71-72°C, which was used without further purification. Crystallization of an aliquot from hexane provided the analytical sample, mp 72-73°C.

Anal. Calcd. for $C_{23}H_{23}F_3N_2O_4$: C, 61.60; H, 5.17; N, 6.25.
Found: C, 61.36; H, 5.29; N, 6.40

8-Amino-6-methoxy-4-methyl-5-[5-(4-trifluoromethylphenyl)pentoxy]quinoline (42)

The reduction of 33 was effected essentially as described for the 2-isomer (30). The yield of the 8-amino derivative (42) from 8.42 g (0.0188 mol) of 33 was 6.37 g (81%). Crystallization of an aliquot from hexane afforded the analytical sample, mp 77-78°C.

Anal. Calcd. for $C_{23}H_{25}F_3N_2O_2$: C, 66.01; H, 6.02; N, 6.70.
Found: C, 65.86; H, 6.34; N, 6.66.

6-Methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)-5-[5-(4-trifluoromethylphenyl)pentoxy]quinoline (51)

Phthalimidoalkylation of 5.85 g (0.014 mol) of 42, carried out as described for the synthesis of 48, gave 4.82 g (54%) of 51 as an orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5-[5-(4-trifluoromethylphenyl)pentoxy]quinoline Fumarate (60)

A stirred solution of 51 (4.82 g, 0.0076 mol), $CHCl_3$ (30 ml), EtOH (60 ml) and 95% NH_2NH_2 (6 ml) was heated under reflux for 1 h, allowed to cool and filtered. The white residue was washed with EtOH (5 ml) and the combined filtrate and washings were concentrated to an orange oil. The oil was dissolved in Et_2O (200 ml) and the solution was washed with 25% KOH (3 x 50 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and concentrated to a dark orange oil; yield 3.61 g (94%) after pumping for 1 h at 1 mm/Hg. This base was dissolved in CH_3CN (20 ml) and slowly treated, during 15 min, with 35 ml of a hot solution of fumaric acid (0.83 g) in MeOH-CH_3CN (1:1 v/v). The resulting solid was washed with CH_3CN (2 x 25 ml), crystallized from CH_3CN and dried (3.5 h at 0.5-1.0 mm) to give 2.86 g (61%) of 60 as a yellow solid, mp 155-156°C (decomp.).

Anal. Calcd. for $C_{32}H_{40}F_3N_3O_6$: C, 62.02; H, 6.51; N, 6.78.
Found: C, 61.75; H, 6.81; N, 6.57.

1-Bromo-5-(4-methylphenyl)pentane(24)

To a stirred solution of 6 (25.66g, 0.15 mol) in THF (120 ml) and hexane (60 ml) at -40°C, under N_2, was slowly added, during 40 min, 60 ml (0.15 mol) of a 2.5 M solution of BuLi in hexane (Aldrich). Stirring was continued for 20 min while the temperature was allowed to rise to -10°C and the mixture was then treated with 1,5-dibromopentane (Aldrich; 34.5g, 0.15 mol) during 10 min. After gradual warming to room temperature, the mixture was stirred for 4h, cooled to 0°C and slowly added to water-ice (200 ml). The aqueous layer was extracted with Et_2O (3 x 100 ml) and the combined extracts and organic layer were washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4) and concentrated to a pale yellow oil. Fractional distillation gave 16.2g (45%) of 24 as a colorless oil, bp 102°C/0.8 mm; n_D^{23} 1.5272.

Anal. Calcd. for $C_{12}H_{17}Br$: C, 59.76; H, 7.11.
Found: C, 59.92; H, 7.13.

6-Methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]-8-nitroquinoline (34)

To a stirred mixture of 28 (WRAIR; 13.75g, 0.059 mol), 24 (14.16g, 0.059 mol) and HMPA (40 ml), at 115-120°C, was added dropwise, during 75 min, a solution of Et_3N (8 ml) and propylene oxide (24 ml). The mixture was heated at 125-130°C for 7 h, allowed to cool and exhaustively extracted with pet ether (20-40°C) and Et_2O (1:1, 400 ml). The combined extracts were washed with 10% NaOH (3 x 100 ml) and the washings were re-extracted with Et_2O (3 x 75 ml). The combined Et_2O solutions were washed with H_2O (3 x 100 ml), dried (Na_2SO_4), treated with carbon (Darco) and concentrated to a dark yellow oil. The oil was pumped at 0.6 mm for 1 h and the resulting semi-solid was vigorously triturated with hexane (15 ml) at 5°C to give a yellow solid. Washing with hexane (2 x 10 ml) gave 12.85g (56%) of 34 as a yellow solid which was used without further purification. Crystallization of an aliquot from hexane provided the analytical sample, m.p. 59-60°C.

Anal. Calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64.; N, 7.10.
Found: C, 69.93; H, 6.80; N, 6.99.

8-Amino-6-methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]quinoline (43)

A stirred mixture of 34 (11.70g, 0.030 mol), Fe filings (12g), Bu_2O (30 ml), H_2O (100 ml) and HOAc (1.5 ml) was heated at 115-120°C for 3.5 h, allowed to cool and the supernatant portion decanted. The solid and the decantate were extracted with Et_2O and the combined extracts were washed with saturated NaCl solution (2 x 100 ml), dried (Na_2SO_4), treated with carbon (Darco) and concentrated to a dark oil. The oil was pumped (1mm/Hg) for 3 h at room temperature, cooled to 0°C and vigorously triturated with hexane (20 ml) to give a yellow solid. The solid was washed with hexane to give 8.73g (81%) of 43 which was used without further purification. Crystallization of an aliquot from hexane afforded the analytical sample as yellow crystals, m.p. 56-57°C.

Anal Calcd. for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69.
Found: C, 75.67; H, 7.84; N, 7.63.

6-Methoxy-4-methyl-5-[5-(4-methylphenyl)pentoxy]-8-(1-methyl-4-phthalimidobutylamino)quinoline (52)

A stirred mixture of 43 (7.12 g, 0.0195 mol) and 4-bromo-1-phthalimidopentane (BPP) (12.36g, 0.042 mol) was heated at 120-125°C while Et_3N (4 ml) was slowly added during 45 min. After 3h at 120-125°C, more BPP (8.87 g, 0.03 mol) and Et_3N (3 ml during 30 min.) were added and heating was continued for 5h. On cooling, the mixture was exhaustively extracted with Et_2O (300 ml) and the extract was washed with saturated brine (2 x 100 ml), dried (Na_2SO_4) and concentrated to a deep orange oil. The oil was pumped at 1 mm Hg for 1.5 h, applied to a silica gel column and eluted with $CHCl_3$. Concentration of the product eluates gave 11.25 g (99%) of 52 as an orange oil which was pumped at 0.8 mm Hg for 1h and used without further purification.

8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5[5-(4-methylphenyl)pentoxy]quinoline Fumarate (61)

A stirred solution of 52 (11.25 g, 0.0194 mol), $CHCl_3$ (50 ml), EtOH (100 ml) and 95% NH_2NH_2 (6 ml) was heated under reflux for 2.5 h, allowed to cool and filtered. The white residue was washed with EtOH and the combined filtrate and washings were evaporated to an orange oil. The oil was dissolved in Et_2O (250 ml) and the solution was washed with 25% KOH (3 x 75 ml), saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4) and concentrated to a viscous yellow oil (6.48 g, 74%). The oil was dissolved in CH_3CN (25 ml) and slowly added to a hot solution of fumaric acid (1.67 g) in CH_3OH-CH_3CN (1:4 v/v, 65 ml). The resulting yellow precipitate was separated by decantation, washed with CH_3CN (3 x 20 ml), recrystallized from CH_3CN and vacuum dried (0.8 mm, 20°C, 2h) to give 5.6 g (51%) of 61 as a yellow solid, mp 153-154 (decomp.)

Anal Calcd. for $C_{32}H_{43}N_3O_6$: C, 67.94; H, 7.66; N, 7.43.

Found: C, 67.82; H, 7.75; N,7.25

1-Bromo-5-(4-methoxyphenyl)pentane (25)

This synthesis was carried out in a manner identical with that described for the preparation of 21. From 37.4 g (0.20 mol) of 7 was obtained 18.0 g (35%) of 25 as a colorless oil, bp 125-127°C/1mm; n_D^{24} 1.5339. This material was used without further purification.

5-[5-(4-Methoxyphenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (35)

To a stirred mixture of 28 (7.5 g, 0.032 mol), 25 (8.24 g, 0.32 mol) and HMPA (25 ml), at 125-130°C, was added, dropwise during 75 min, a solution of propylene oxide (25 ml) and Et_3N (6 ml). The mixture was heated for an additional 6 h, allowed to cool, extracted with Et_2O (350 ml) and Me_2CO to leave 3.83 g of unreacted starting material 28. The ether extract was washed with 5% NaOH (2 x 75 ml), H_2O (3 x 100 ml), dried (Na_2SO_4) and concentrated to a black oil. The oil was placed on a silica gel column and eluted with $CHCl_3$. Evaporation of the early eluates returned 4.47 g of the starting material, 25. Subsequent eluates provided 3.51 g (27%) of 35 as a viscous yellow oil which was used without further purification.

8-Amino-5-[5-(4-methoxyphenyl)pentoxy]-6-methoxy-4-methylquinoline (44)

A stirred mixture of 35 (5.0 g, 0.012 mol), Bu_2O (10 ml), H_2O (75 ml), HOAc (1 ml) and Fe filings (5 g) was heated at 110-115°C for 3 h, allowed to cool and filtered. The filtrate and the solid were extracted with Et_2O (300 ml) and the combined extracts were washed with saturated sodium chloride solution (2 x 50 ml), dried (Na_2SO_4) and concentrated in vacuo. The resulting dark solid was placed on a silica gel column and eluted with 1% MeOH in $CHCl_3$. Concentration of the eluates gave 3.84 g (83%) of 44 as a viscous oil which solidified on standing. This material was used without further purification.

5-[5-(4-Methoxyphenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (53)

A stirred mixture of 44 (3.58 g, 0.0094 mol) and 4-bromo-1-phthalimidopentane (BPP) (5.58 g, 0.0188 mol) was heated at 120-125°C while Et_3N (2.5 ml) was added during 20 min. The mixture was heated for an additional 3 h, allowed to cool, placed on a silica gel column and eluted with $CHCl_3$. Concentration of the eluates left 3.32 g, (60%) of 53 as an oil which was used without further purficiation.

8-(4-Amino-1-methylbutylamino)-5-[5-(4-methoxyphenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (62)

A stirred solution of 53 (4.6 g, 0.0079 mol), $CHCl_3$ (30 ml), EtOH (60 ml) and 95% NH_2NH_2 (10 ml) was heated under reflux for 2 h, allowed to cool and filtered. The solid was washed with a small amount of EtOH and the combined filtrate and washings were concentrated to a dark orange oil. The oil was dissolved in Et_2O (200 ml), washed with 25% KOH (3 x 75 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and concentrated to a deep yellow oil. The oil was dissolved in CH_3CN (30 ml) and treated with 40 ml of a hot solution of fumaric acid (0.75 g) in MeOH-CH_3CN (1:4). Crystallization of the resulting solid from CH_3CN gave 2.54 g (55%) of 62 as a yellow solid, m.p. 152-153°C (decomp.).
Anal. Calcd. for $C_{32}H_{43}N_3O_7$; C, 66.07; H, 7.45; N, 7.22.
Found: C, 65.85; H, 7.68; N, 7.08

1-Bromo-5-[4-(methylthio)phenyl]pentane (67)

To a stirred solution of 65 (Aldrich; 20.3 g, 0.1 mol), THF (120 ml) and hexane (60 ml), at -40°C, under N_2, was slowly added, during 40 min, 40 ml (0.1 mol) of a 2.5 M solution of BuLi in hexane (Aldrich). The stirred white suspension was allowed to warm to -10°C during 20 min and treated, during 10 min, with 1,5-dibromopentane (23.0 g, 0.1 mol). The mixture was allowed to warm to room temperature, stirred for 3h, cooled to 0°C and slowly added to water-ice (200 ml). The aqueous layer was extracted with Et_2O (2 x 150 ml) and the combined extracts and organic layer were washed with saturated NaCl solution (2 x 75 ml), dried (Na_2SO_4) and concentrated to a pale yellow oil.

The fraction boiling below 104°C/2mm was distilled off and the residue was applied to a silica gel column. Elution with hexane and concentration of the eluates gave 7.0 g (26%) of 67 as a colorless oil (n_D^{24} 1.5660) which was used without further purification.

1-Bromo-5-[4-(methylsulfonyl)phenyl]pentane (26)

To a stirred solution of 67 (6.4 g, 0.023 mol) in CH_2Cl_2 (50 ml), at -5°C to 0°C, was added, during 45 min, a solution of 3-chloroperbenzoic acid (Aldrich, 85%; 9.34 g, 0.046 mol) in CH_2Cl_2 (100 ml). The mixture was allowed to warm gradually to room temperature, stirred for 2 h and filtered. The white residue was washed with CH_2Cl_2 (3 x 20 ml) and the combined organic layers were washed with 10% $NaHCO_3$ (3 x 75 ml), saturated NaCl solution (2 x 50 ml), dried (Na_2SO_4) and concentrated to a viscous oil. Trituration with cold hexane gave 6.0 g (86%) of 26 as a white solid, mp 43-44°C.

In a similar experiment, the colorless viscous oil was eluted from a silica gel column (EtOAc-Hexane; 1:3 v/v). The product eluates were kept in the freezer overnight and the resulting crystals were washed with hexane and dried in vacuo (2 h, room temp., 0.5 mm) to give the analytical sample, mp 45-46°C.

Anal. Calcd. for $C_{12}H_{17}BrSO_2$: C, 47.21; H, 5.62; O, 10.48
Found: C, 47.16; H, 5.51; O, 10.59

6-Methoxy-4-methyl-5-[5-(4-methylsulfonylphenyl)pentoxy]-8-nitroquinoline (36)

To a stirred mixture of 28 (WRAIR; 1.54g, 0.007 mol), 26 (2.00g, 0.007 mol) and HMPA (20 ml), at 115-120°C, was added dropwise, during 45 min., a solution of Et_3N (2 ml) and propylene oxide (8 ml). Heating was continued for 7h and after cooling, the mixture was exhaustively extracted with ethyl acetate (200 ml). The combined extracts were washed with 10% NaOH solution (3 x 50 ml) and the basic wash solution was re-extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with saturated NaCl solution (3 x 50 ml), dried (Na_2SO_4), concentrated (25 ml) and diluted with hexane (40 ml). On cooling (-5°C) the solution overnight, a yellow solid precipitated which was filtered, washed with hexane and air-dried to give 2.11 g (70%) of 36 as a yellow solid which was used without further purification.

Crystallization of an aliquot from ethyl acetate-hexane provided the analytical sample as pale yellow crystals, m.p. 123-124°C.
Anal. Calcd. for $C_{23}H_{26}N_2O_6S$: C, 60.24; H, 5.72, N, 6.11.
Found: C, 60.40; H, 5.97; N, 5.96

1-Bromo-5-(4-chloro-3-trifluoromethylphenyl)pentane (27)

To a stirred solution of 9 (Aldrich; 25.95 g, 0.1 mol) in anhydrous Et_2O (120 ml), under N_2, at -20°C, was added dropwise, during 20 min, 40 ml of a 2.5 M solution of BuLi in hexane (Aldrich). Stirring was continued for 30 min. and the mixture was then treated, dropwise, during 15 min, with 1,5-dibromopentane (Aldrich; 23.0 g, 0.1 mol). The mixture was allowed to warm to 0°C, stirred for 2 h and then treated, at 0°C, during 20 min, with THF (60 ml). After gradual warming to room temperature, the mixture was stirred for 2 h, poured slowly onto crushed dry ice (100 g) and carefully added to H_2O (150 ml). The aqueous layer was extracted with Et_2O (3 x 125 ml) and the combined extracts and organic layer were washed with 10% Na_2CO_3 (3 x 100 ml) and saturated NaCl solution (3 x 100 ml), dried (Na_2SO_4) and concentrated to a dark oil. Fractional distillation gave 5.0 g (15%) of 27 as an oil, bp 136-138°C/2 mm; n_D^{25} 1.5019.

5-[5-(4-Chloro-3-trifluoromethylphenyl)pentoxy]-6-methoxy-4-methyl-8-nitroquinoline (37)

To a stirred mixture of 28 (WRAIR; 3.49 g, 0.015 mol), 27 (4.92 g, 0.015 mol) and HMPA (20 ml), at 110-115°C, was added dropwise, during 1 h, a solution of propylene oxide (16 ml) and Et_3N (4 ml). The mixture was heated at 120-125°C for 4 h and at 135-140° for 1 h, allowed to cool and extracted with a 1:1 mixture (250 ml) of pet ether and Et_2O. The extract was washed with 10% NaOH (3 x 100 ml), H_2O (3 x 100 ml), saturated NaCl (2 x 50 ml), dried (Na_2SO_4) and concentrated to give 4.71 g (66%) of 37 as a yellow solid which was used without further purification. Crystallization of an aliquot from hexane gave an analytical sample as yellow crystals, mp 91-92°C.
Anal. Calcd. for $C_{23}H_{22}ClF_3N_2O_4$: C, 57.20; H, 4.59; N, 5.80.
Found: C, 56.99; H, 4.72; N, 5.[illegible]

8-Amino-5-[5-(4-chloro-3-trifluoromethylphenyl)pentoxy]-6-methoxy-4-methylquinoline (46)

A stirred mixture of 37 (6.52 g, 0.0135 mol) Bu_2O (15 ml), H_2O (75 ml), Fe filings (6 g) and AcOH (1 ml) was heated at 110-115°C for 2 h, allowed to cool and filtered. The solid and the filtrate were extracted with Et_2O and the combined extracts were washed with saturated NaCl solution, dried (Na_2SO_4), treated with carbon (Darco) and concentrated to an oil. The latter was pumped at room temperature for five hours at 0.2 mm to leave 4.63 g (76%) of 46 as a yellow solid which was used without further purification.

5-[5-(4-Chloro-3-trifluoromethylphenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (55)

A stirred mixture of 46 (1.8 g, 0.004 mol) and 4-bromo-1-phthalimidopentane (BPP) (2.36 g, 0.008 mol) was heated at 125-130°C while Et_3N (1 ml) was slowly added during 15 minutes. Heating was continued for 3 h, and the mixture was allowed to cool, placed on a silica gel column and eluted with $CHCl_3$. Concentration gave 2.34 g (88%) of 55 as a viscous yellow oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(4-chloro-3-trifluoromethylphenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (64)

A stirred mixture of 55 (1.41 g, 0.002 mol), $CHCl_3$ (20 ml), EtOH (40 ml) and 95% NH_2NH_2 (6 ml) was heated under reflux for 2 h, allowed to cool and filtered. The residue was washed with EtOH (5 ml) and the combined filtrate and washings were concentrated in vacuo. The residue was dissolved in Et_2O (100 ml) and the solution was washed with 25% KOH (3 x 30 ml) and saturated NaCl (2 x 50 ml), dried (Na_2SO_4) and concentrated to a crude dark yellow oil (1.13 g, 100%). This material was dissolved in CH_3CN (10 ml) and slowly treated with a boiling solution of 0.24 g of fumaric acid in 12 ml of a 1:4 v/v solution of MeOH and CH_3CN. The resulting solid was separated by decantation, washed with CH_3CN (3 x 10 ml) and crystallized from CH_3CN to give 0.89 g (65%) of 64 as a yellow solid, mp 152-153°C (decomp.).
Anal. Calcd. for $C_{32}H_{40}F_3N_2O_6$: C, 58.75; H, 6.01; N, .42.
Found: C, 58.52; H, 6.16; N, 6.72

8-Amino-5-(3-chlorophenyl)pentoxy]-6-methoxy-4-methylquinoline (72)

The sequence from 68 to 72 (Scheme 3) was a simple repetition of the one used in our initial synthesis of 72 (Annual/Final Report, USAMRDC Contract No. DAMD17-86-C-6094, February 1988, pp. 90-91).

5-[5-(3-Chlorophenyl)pentoxy]-6-methoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)quinoline (73)

A stirred mixture of 72 (9.8 g, 0.025 mol) and BPP (15 g, 0.05 mol) was heated at 125-130°C while Et_3N (5 ml) was added dropwise. Additional quantities of BPP (15 g) and Et_3N (5 ml) were introduced twice more at 2 h intervals while maintaining the temperature at 125-130°C. The mixture was allowed to cool and extracted with Et_2O. The extract was washed with saturated NaCl, dried (Na_2SO_4), treated with Darco G-60 and concentrated to a brown syrup. This material was diluted with $CHCl_3$ and passed through a silica gel column. Concentration of the eluates gave 6.6 g of 73 as a viscous orange oil which was used without further purification.

8-(4-Amino-1-methylbutylamino)-5-[5-(3-chlorophenyl)pentoxy]-6-methoxy-4-methylquinoline Fumarate (74)

The conversion of the phthalimido precursor 73 to 74 was carried out in a manner identical with that described previously (Annual/Final Report, USAMRDC Contract No. DAMD17-86-C-6094, February 1988, pp. 90-91).

6-Methoxy-4-methyl-8-nitro-5-phenoxyquinoline (78)

A solution of phenol (76) (11.1 g, 0.12 mol), NaOH (4.8 g, 0.12 mol) and EtOH (150 ml) was heated under reflux for 2 h and the solvent was evaporated. To the white residue of sodium phenoxide was added 75 (WRAIR; 25.3 g, 0.1 mol) in dioxane (150 ml) and the mixture was heated under reflux for 26 h, allowed to cool, diluted with Me_2CO (200 ml) and filtered. The black residue was washed with Me_2CO (100 ml) and the combined filtrate and washings were concentrated to a dark brown syrup which was extracted with $CHCl_3$.

The extract was washed with 20% KOH and NaCl solution, dried (Na_2SO_4) and passed through a silica gel column. Concentration gave 21.5 g (69%) of 78 as yellow needles, m.p. 150-170°C, which was used without further purification (Lit.[4], m.p. 169-171°C).

8-Amino-6-methoxy-4-methyl-5-phenoxyquinoline (80)

A stirred mixture of 78 (29.6 g, 0.09 mol) Fe filings (40 g), H_2O (300 ml), HOAc (5 ml) and Bu_2O (20 ml) was heated under reflux for 5 h, allowed to cool and filtered. The filtrate and the residue were extracted with Et_2O and the combined extracts were washed with saturated NaCl, dried (Na_2SO_4), treated with Darco G-60 and concentrated, in vacuo, to a yellow-green semi-solid. Trituration of this material with Et_2O gave 12.9 g (51%) of 80 as a yellow solid, mp 151-156°C, which was used without further purification. Crystallization of an aliquot from hexane-benzene (9:1) (Darco G-60) provided the analytical sample as yellow needles, mp 155-157°C.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84, H, 5.75; H, 9.99.
Found: C, 72.74; H, 5.88; N, 10.28

6-Methoxy-4-methyl-5-phenoxy-8-phthalimidoquinoline (82)

A mixture of 80 (18.8 g, 0.067 mol), phthalic anhydride (10 g, 0.067 mol) and xylene (300 ml) was refluxed for 24 h with water collection in a Dean-Stark trap. The mixture was allowed to cool and filtered to give 10.2 g of 82 as a gray solid which melted at 223.5-225°C after washing with xylene. This material was used without further purification. Crystallization of an aliquot from toluene gave the analytical sample as white platelets, mp 225-226.5°C.

Anal. Calcd. for $C_{25}H_{18}N_2O_4$: C, 73.16; H, 4.42; N, 6.82.
Found: C, 73.38; H, 4.42; N, 6.82

6-Methoxy-4-methyl-5-phenoxy-8-phthalimidoquinoline-1-oxide (84)

To a stirred solution of 82 (13.8 g, 0.03 mol) in $CHCl_3$ (200 ml), at 2-5°C, was added, during 0.5 h, a solution of 3-chloroperbenzoic acid (Aldrich, 80-85%; 7.3 g, 0.03 mol) in $CHCl_3$ (100 ml). The mixture was stirred for 1 h, allowed to warm to room temperature overnight, washed with 5% $NaHSO_3$ (10 ml), dried (Na_2SO_4) and placed on a basic alumina column. Elution with $CHCl_3$-MeOH (98:2) and concentration of the eluates gave 10 g of crude 84. Extraction of this material with hot EtOH and concentration of the extract gave 6.5 g (46%) of 84 as yellow crystals, mp 234-237°C. This material was used without further purification.

2-Chloro-6-methoxy-4-methyl-5-phenoxy-8-phthalimidoquinoline (86)

To a stirred solution of 84 (9.7 g, 0.02 mol) in $CHCl_3$ (150 ml), at 0°C, was added dropwise, during 15 min, 20 ml (0.2 mol) of $POCl_3$. The solution was heated under reflux for 2 h, allowed to cool, poured over ice and basified with 20% NaOH. The aqueous layer was extracted with $CHCl_3$ and the combined extracts and organic layer were washed with saturated $NaHCO_3$ and H_2O, dried ($MgSO_4$) and concentrated to a yellow syrup. Crystallization from EtOH gave 8.6 g (97%) of 86 as pale yellow needles, mp 247-249°C.

Anal. Calcd. for $C_{25}H_{17}ClN_2O_4$: C, 67.50; H, 3.85; N, 6.30
Found: C, 67.76; H, 3.88; N, 6.10

8-Amino-2-chloro-6-methoxy-4-methyl-5-phenoxyquinoline (88)

A stirred suspension of 86 (8.3 g, 0.01 mol), 95% NH_2NH_2 (20 ml) and EtOH (500 ml) was refluxed for 3 h, allowed to cool and filtered. The white solid was washed with EtOH and CH_2Cl_2 and the combined filtrate and washings were concentrated. The resulting suspension was extracted with CH_2Cl_2 and the extract was washed with 20% NaOH, saturated NaCl solution, dried (K_2CO_3) and concentrated to yellow gum. Crystallization from hot toluene-hexane (1:1) gave 5.6 g (99%) of 88 as yellow needles, mp 177.5-179°C.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90.
Found: C, 64.98; H, 4.86; N, 8.85

8-Amino-2,6-dimethoxy-4-methyl-5-phenoxyquinoline (90)

A solution of 88 (4 g, 0.01 mol) in MeOH (50 ml) was added dropwise to a MeONa-MeOH solution (prepared from 0.8 g of Na and 150 ml of MeOH) at room temperature and the resulting orange solution was refluxed for 40 h, cooled and concentrated to an orange syrup. The syrup was diluted with CH_2Cl_2 and chromatographed (SiO_2; CH_2Cl_2: MeOH, 100:1). The yellow product eluate was collected, concentrated to a light brown oil and triturated with hexane to provide 2.3 g (61%) of 90, m.p. 93-98°C. Crystallization from ethanol provided the analytical sample as pale tan crystals, m.p. 95-97°C.
Anal Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03
Found: C, 70.12; H, 6.09; N, 9.01

2,6-Dimethoxy-4-methyl-8-(1-methyl-4-phthalimidobutylamino)-5-phenoxyquinoline (92)

A stirred mixture of 90 (2.3 g, 0.007 mol) and BPP (5 g, 0.016 mol) was heated at 125°C while Et_3N (3 ml) was added, dropwise, during 0.5 h. After 2 h, a second portion of BPP (5 g) was added followed by slow introduction of more Et_3N (3 ml). Addition of BPP (5 g) and Et_3N (3 ml) was repeated twice more at 2 h intervals. The mixture was allowed to cool and extracted with Et_2O (300 ml). Evaporation of the extract left an oil which was dissolved in a small amount of CH_2Cl_2, placed on a silica gel column (250 g) and eluted with CH_2Cl_2. The early eluates contained unreacted BPP and were discarded. Subsequent eluates were combined, concentrated and triturated with EtOH. The resulting solid (2 g, m.p. 134-137°C) was used without further purification.

5-(4-Fluorophenoxy)-6-methoxy-4-methyl-8-nitroquinoline (79)

A mechanically stirred mixture of 77 (Aldrich, 12.16g, 0.108 mol), potassium hydroxide (6.18g, 0.091 mol) and 2-ethoxyethanol (27 ml) was heated at 90°C for 1 h. 75 (WRAIR, 19.00g, 0.075 mol) in 2-ethoxyethanol (22 ml) was added rapidly and the mixture was heated at 120°C for 1 h followed by cooling at 0°C for 1 h. The precipitate was filtered, washed with cold EtOH and suspended in H_2O (100 ml).

After stirring for 5 min, the mixture was filtered and the residue was washed with cold EtOH followed by pet ether (20-40°C). Air-drying gave 19.92 g (81%) of 79 as a yellow solid, m.p. 179-181°C (Lit.[5], m.p. 183.5-185°C). This material was used without further purification.

8-Amino-5-(4-fluorophenoxy)-6-methoxy-4-methylquinoline (81)

A mechanically stirred mixture of 79 (19.90 g, 0.067 mol), Fe filings (20 g), Bu_2O (75 ml), H_2O (150 ml) and HOAc (2 ml) was heated at 110-115°C for 5 h, allowed to cool and filtered. The filtrate was extracted with Et_2O (200 ml) and the combined extracts were washed with saturated NaCl solution (2 x 75 ml), dried ($MgSO_4$) and concentrated to a small volume. The precipitated solid was filtered, washed with hexane and air-dried to give 2.71 g (15%) of 81 as a yellow solid, m.p. 147-148°C (Lit.[5], m.p. 144.5-145.5°C). The residue from the reaction mixture was stirred with $CHCl_3$ (250 ml) for 5 min and filtered. The filtrate was washed with saturated NaCl solution (2 x 75 ml), dried (K_2CO_3), treated with Darco and evaporated to give another crop of 81, m.p. 147-148°C (12.33 g, 68%). The combined material was used without further purification.

5-(4-Fluorophenoxy)-6-methoxy-4-methyl-8-phthalimidoquinoline (83)

A mixture of 81 (15.00 g, 0.05 mol) and phthalic anhydride (Aldrich; 8.18 g, 0.055 mol) in xylene (200 ml) was refluxed for 20 h using a Dean-Stark water removal trap. The reaction mixture was cooled (0-5°C) for 1 h and filtered. The residue was washed with pet ether (20-40°C) and air-dried to yield 17.30 g (80%) of a greyish white solid, m.p. 214-215°C (Lit.[6] m.p. 213-215°C). The mother liquor was diluted with pet ether (20-40°C, 100 ml) and cooled (0°C) overnight. The precipitated solid was filtered, washed with pet ether (20-40°C) and air-dried to give another crop (2.17 g, 10%) of 83 as a greyish white solid m.p. 213-214°C. The combined material was used without further purification.

5-(4-Fluorophenoxy)-6-methoxy-4-methyl-8-phthalimidoquinoline-1-oxide (85)

To a mechanically stirred solution of 83 (17.00 g, 0.04 mol) in $CHCl_3$ (100 ml) at 0°, was added, dropwise over 15 min, m-chloroperbenzoic acid (Aldrich, 85%; 16.10 g, 0.08 mol) in $CHCl_3$ (160 ml). The mixture was slowly brought to room temperature, stirred for an additional 16 h, washed with 10% K_2CO_3 solution (3 x 100 ml), H_2O (2 x 100 ml) and dried (K_2CO_3). Solvent evaporation gave a yellow mass which on trituration with cold EtOH (20 ml), yielded a yellow solid. It was filtered, washed with cold EtOH, pet ether (20-40°C) and air-dried to give 17.09 g (97%) of 85 as a pale yellow solid, m.p. 223-225°C (decomp.)(Lit.[6], m.p. 241-243°C). This material was used without further purification.

2-Chloro-5-(4-fluorophenoxy)-6-methoxy-4-methyl-8-phthalimidoquinoline (87)

To a cooled (0-5°C) solution of 85 (17.00 g, 0.038 mol) in $CHCl_3$ (225 ml), was added dropwise, over a period of 15 min, phosphorus oxychloride (Aldrich, 58.64 g, 0.38 mol, 35.7 ml). The orange solution was heated under reflux for 2.5 h, cooled and slowly poured over a bed of ice (200 g). The stirred mixture was treated very slowly with 20% KOH solution (ca. 650 ml) to adjust the pH to 10-11. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 x 200 ml). Combined organic layers were washed with H_2O (2 x 250 ml) and dried ($MgSO_4$). Solvent evaporation and air drying gave 15.00 g (85%) of 87 as a pale yellow solid, m.p. 228-230°C (decomp.) (Lit.[6] m.p. 234-236°C). This material was used without further purification.

8-Amino-2-chloro-5-(4-fluorophenoxy)-6-methoxy-4-methylquinoline (89)

A mixture of 87 (15.00 g, 0.0324 mol), $CHCl_3$ (30 ml), EtOH (120 ml) and 95% NH_2NH_2 (Eastman, 5 ml) was heated under reflux for 3 h, allowed to cool and filtered. The white residue was washed with EtOH and $CHCl_3$ and the combined filtrate and washings were evaporated to an orange oil. The oil was treated with 20% KOH solution (60 ml) and the mixture was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were washed with saturated NaCl solution (2 x 75 ml) and dried (K_2CO_3). Solvent evaporation gave a greenish-yellow solid, 9.29 g (86%), m.p. 145-146°C (Lit.[6], m.p. 150-152°C). This material was used without further purification.

8-Amino-2,6-dimethoxy-5-(4-fluorophenoxy)-4-methylquinoline (91)

A stirred mixture of 89 (3.81 g, 0.0115 mol), sodium methoxide (Aldrich, 0.90 g, 0.017 mol) and anhydrous DMF (25 ml) was slowly brought to 80°C over a period of 45 min, kept at 80°C for another 15 min, cooled and slowly poured over a bed of ice (150 g). The mixture was brought to room temperature, filtered and the residue was taken into CH_2Cl_2 (150 ml). The organic layer was washed with H_2O (2 x 50 ml), dried (K_2CO_3) and concentrated to a black oil. The oil was applied to a silica gel column and eluted with CH_2Cl_2. Concentration of the product eluates gave a yellow oil which on trituration with hexane (5 ml) produced a yellow solid, 2.37 g (64%), m.p. 91-92°C (Lit.[6], m.p. 93-95°C). This material was used without further purification.

2,6-Dimethoxy-5-(4-fluorophenoxy)-4-methyl-8-(1-methyl-4-phthalimidobutylamino) quinoline (93)

A stirred mixture of 91 (3.50 g, 0.011 mol) and 4-bromo-1-phthalimidopentane (BPP) (6.50 g, 0.022 mol) was heated at 105-110°C while Et_3N (3 ml) was slowly added during 15 min. After 4 h at 120-125°C, more BPP (4.00 g, 0.0135 mol) and Et_3N (1.5 ml during 10 min) were added and heating was continued for 5 h. On cooling, the mixture was exhaustively extracted with Et_2O (150 ml). The extract was washed with saturated NaCl solution (2 x 75 ml), dried (K_2CO_3) and concentrated to an orange oil The oil was applied to a silica gel column and eluted with $CHCl_3$. Concentration of the product eluates gave 4.1 g (71%) of 93 as an orange oil which was used without further purification.

5-Benzyloxy-6-methoxy-4-methyl-8-nitroquinoline (97)

A mixture of 28 (35.1 g, 0.15 mol), benzyl bromide (96)(51.3 g, 0.3 mol) and HMPA (50 ml) was heated at 120°C while a mixture of 7.5 ml of Et_3N and 50 ml of propylene oxide was added during 2 h. Heating was continued for 6 h and the mixture was cooled and extracted with Et_2O (500 ml). The insoluble portion was extracted with acetone (100 ml) and the combined Et_2O and Me_2CO extracts were concentrated to a dark brown oil. The oil was diluted with CH_2Cl_2 (500 ml), washed with 10% NaOH and H_2O, dried (Na_2SO_4) and chromatographed (SiO_2, CH_2Cl_2) to give an orange solid. Crystallization from toluene provided 25 g (51%) of 97 as yellow needles, m.p. 132-137°C (Lit.[7], m.p. 137-138°C).

8-Amino-5-benzyloxy-6-methoxy-4-methylquinoline (98)

A stirred mixture of 97, (21 g, 0.06 mol), Fe filings (31 g), H_2O (350 ml), HOAc (5 ml), and n-Bu_2O (50 ml) was heated at 90° for 5 h, cooled and filtered. The residue was washed with H_2O and filtrate and residue were extracted with CH_2Cl_2.

The extract was washed with H_2O, dried (K_2CO_3), concentrated and chromatographed (SiO_2; $CH_2Cl_2 \rightarrow CH_2Cl_2$:MeOH) to give a brown oil. The oil (crude 98, 19 g, 100%) was used for the next step without further purification. (Lit.[7], m.p. 77-78°C)

5-Benzyloxy-6-methoxy-4-methyl-8-phthalimidoquinoline (99)

A mixture of crude 98 (19 g, 0.06 mol), phthalic anhydride (11 g, 0.07 mol), and xylene (500 ml) was refluxed with a Dean-Stark water trap for 24 h, cooled and filtered. Recrystallization of the solid from xylene provided 13 g of 99 as brown-gray platelets, m.p. 220-223°C. Concentration and chromatography (SiO_2, $CHCl_3$) of the filtrates followed by recrystallization provided additional 99 (3 g), m.p. 232-234°C.; total yield, 16 g (63%). Recrystallization from toluene (2x) provided the analytical sample as light tan crystals, m.p. 231-232°C.
Anal. Calcd for $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60.
Found: C, 73.76; H, 4.85; N, 6.61

5-Benzyloxy-2,4-dimethyl-6-methoxy-8-nitroquinoline (119)

To a stirred mixture of 117 (WRAIR; 10 g, 0.04 mol), 118 (Aldrich; 6.9 g, 0.04 mol) and HMPA (20 ml), at 115°C, was added dropwise, during 3 h, a solution of Et_3N (1 ml) and propylene oxide (10 ml). Heating was continued for 4.5 h and after cooling, the mixture was extracted with Et_2O (300 ml); the residue was washed with Me_2CO leaving a tan solid (A). The combined extracts and washings were concentrated to a tar which was dissolved in $CHCl_3$, placed on a silica gel column and eluted with $CHCl_3$. Concentration of the eluates gave a tan solid (B). Crystallization of solids A and B from toluene gave 9.1 g (67%) of 119 as yellow needles, mp 167-170°C.
Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28.
Found: C, 67.24; H, 5.55; N, 8.14.

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ACKNOWLEDGEMENT

We are grateful to Drs. H. A. Musallam and R. R. Engle for assistance, suggestions and enthusiasm during the course of our research.